

A Possible Increase of Activity of Endothelial L-Arginine/Nitric Oxide Pathway in Aortas of Diet-Induced Obesity Rats

Bruder-Nascimento T^{1,2*}, Campos DHS³, Alves CAB³, Cicogna AC³ and Cordellini S²

¹Department de Pharmacology, Scholl of Medicine of Ribeirão Preto, University of São Paulo (USP), Ribeirão Preto, São Paulo, Brazil

²Department de Pharmacology, Institute of Bioscience of Botucatu, São Paulo State University (UNESP), Botucatu, São Paulo, Brazil

³Department of Medicine Clinical, Botucatu School of Medicine, São Paulo State University (UNESP), Botucatu, São Paulo, Brazil

Abstract

The obesity is associated with cardiovascular disorders. The aim of present purpose was test the hypothesis that the diet-induced obesity is able to generate a vascular adaptive response in aortic rings; this response could be mediated by NO pathway.

The present work used Thirty-day-old male *Wistar* rats (70-100 g) were distributed into two groups: control (C) and obese (Ob). The obesity was induced through of hypercaloric diet during 15 weeks, the vascular response was assessed through different protocols of vascular reactivity studies and characterization of obesity was also evaluated.

The obesity was characterized for decreased of glucose tolerance, hyperinsulinemia, hyperleptinemia and rise of adiposity index. In relation to vascular alterations, the diet-induced obesity generated decreased maximal response to noradrenaline, response which was abolished with presence of L-NAME, and increased relaxing to acetylcholine. There was no difference between groups in the blood pressure.

The vascular responses observed in present work might have occurred with the aim of decrease of cardiovascular risk linked with obesity pathology; these findings suggest that obesity can be considered a paradoxical disorder.

Keywords: Diet-induced obesity; Paradoxical obesity; Nitric oxide

Introduction

Obesity is now so common within the world's population that it can replace undernutrition and infectious diseases as the most significant contributor to disorders. Thus, it constitutes a major public health problem [1,2]. Although the etiology of obesity is complex, several factors have been implicated in its development, especially hypercaloric intake [3]. In this context, a variety of experimental models of obesity exist, on the other hand, dietary-induced obesity is the most relevant experimental model regarding to human obesity [4].

The literature has demonstrated that obesity decreases life expectancy and is associated with medical complications, such as type 2 diabetes mellitus, increased incidence of certain forms of cancer, respiratory complications (obstructive sleep apnea), dyslipidemia, hypertension, atherosclerosis and cardiovascular alterations [1,5].

Several authors suggest that the obesity is a paradoxical disorder; patients with chronic disease excess weight are paradoxically associated with a decreased risk of adverse outcomes [6-8].

The mean endothelium-derived relaxing factors (EDRF) are endothelium-derived hyperpolarizing factor (EDHF) [9], prostacyclin [10] and nitric oxide (NO) [11,12]. Alternatively, generation of nitric oxide may be blocked by competitive inhibitors of nitric oxide synthase such as L-nitroarginine (LNA) or L-nitroarginine methyl ester (L-NAME) [13,14]. Thus, this inhibitor could contribute to check the involvement of NO in different protocols among them vascular studies [15].

Besides, there are some controversies with the involvement of NO-pathway on vascular disorders induced by obesity, there is evidence that impairment of NO synthesis represent a central defect triggering many of the vascular abnormalities characteristic of obesity states [16,17]. However, previous experiment of our laboratory suggested that obesity produced increase of NO-pathway activity in concentration-curves effect (CCE) to noradrenaline in aortic rings, since the presence

of L-NAME produced left shift in CCEs to same adrenergic agonist in diet-induced obesity rats [18], this results agree the obesity as a paradoxical disorder.

Given these information the aim of present purpose was test the hypothesis that the diet-induced obesity is able to generate a vascular adaptive response in aortic rings, this response could be mediated by NO pathway trying to counterbalance the deleterious effects of obesity on the vascular system.

Materials and Methods

Animal

Thirty-day-old male *Wistar* rats (~150g) were randomly assigned to one of two groups: control (C) and obese (Ob). The control group was fed a standard rat chow containing 4% fat, 42.7% carbohydrate, and 22% protein; whereas the obese animals received a high-fat diet containing 20% fat, 26.4% carbohydrate, and 20% protein. Each group was fed the diet for 15 (C and Ob; n=16), weeks. High fat diet was designed in our laboratory and contained powdered commercial Agrocere[®] Animal Chow (Rio Claro, SP, Brazil), industrialized feed, protein supplement, vitamins and minerals. The high-fat diet was calorically rich (high-fat diet = 3.65 kcal/g versus standard diet = 2.95 kcal/g) due to the higher fat composition, made with saturated (20%)

***Corresponding author:** Thiago Bruder do Nascimento, Department of Pharmacology, Scholl of Medicine of Ribeirão Preto, University of São Paulo (USP), Ribeirão Preto, São Paulo, Brazil, Fax: +55-16-36332301; E-mail: bruderthiago@usp.com.br

Received November 07, 2011; **Accepted** December 12, 2011; **Published** December 15, 2011

Citation: Bruder-Nascimento T, Campos DHS, Alves CAB, Cicogna AC, Cordellini S (2011) A Possible Increase of Activity of Endothelial L-Arginine/Nitric Oxide Pathway in Aortas of Diet-Induced Obesity Rats. *Endocrinol Metabol Syndrome* S8:001. doi:10.4172/2161-1017.S8-001

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and unsaturated fatty acid (80%). All rats were housed in individual cages in an environmentally-controlled clean-air room at 23±3°C with a 12 h light/dark cycle and 60±5 % relative humidity.

All experiments and procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals, published by the U.S. National Institutes of Health, 1985, and was approved by the Botucatu Medical School Ethics Committee (UNESP, Botucatu, SP, Brazil).

Nutritional, metabolic and endocrine profiles of the animals

To analyze if dietary-induced obesity was associated with alterations in the nutritional behavior, food consumption was measured daily. Weekly calorie intake was calculated by average weekly food consumption \times dietary energetic density. Feed efficiency, the ability to transform calories consumed into BW, was determined by following the formula: mean body weight gain (g)/total calorie intake (kcal).

Since obesity is defined as an excessive amount of body fat in relation to lean mass [19], an adiposity index was considered from sum of several fat pads. After 12-15h fasting, animals were anesthetized with sodium pentobarbital (50 mg/kg) and euthanized by decapitation. Animals were thoracotomized and the total body fat (BF) was measured from the sum of the individual fat pad weights: visceral, epididymal and retroperitoneal. The adiposity index was calculated by ratio total body fat to final body weight \times 100.

The obesity can be accompanied of metabolic and endocrine disturbances [1], glycemic tolerance, leptinemia and insulinemia were analyzed. In relation to glycemic tolerance, after fasting for 12-15h, rats were submitted to a glucose tolerance test (GTT). Blood samples were drawn from the tail at baseline and after administration of glucose (2 g/kg, i.p.) [20,21]. Blood samples were collected at 0, 15, 30, 60, 90 and 120 minutes. Glucose levels were determined using the ACCU-CHEK GO KIT glucose analyzer (Roche Diagnostic Brazil Ltda., Brazil). To biochemical and hormonal analysis, trunk blood was collected in heparinized tubes, centrifuged at 3000 g for 15min at 4°C. Serum leptin and insulin concentrations were determined by ELISA using commercial kits (Linco Research Inc., USA).

Systolic Blood Pressure (SBP)

The evaluation of SBP was assessed by the non-invasive tail-cuff method with a Narco BioSystems' Electro-Sphygmomanometer (International Biomedical, Austin, TX, USA) (Pfeffer et al., 1971) every 3 weeks. The average of two pressure readings was recorded for each animal.

Vascular reactivity

After 15 weeks of high-fat diet or standard rat chow exposure the animals were decapitated. The descending thoracic aorta was excised and trimmed free of adhering fat and connective tissue. Two transverse rings of the same artery, each about 4 mm in length, were cut and mounted at the optimal length for isometric tension recording in organ chambers. One ring served as control, while the endothelium was mechanically removed from the others by gently rubbing the luminal surface [22]. The preparations were mounted in organ baths containing 7 ml of Krebs-Henseleit solution, with composition in mM: NaCl 113.0; KCl 4.7; CaCl₂ 2.5; KH₂PO₄ 1.2; MgSO₄ 1.1; NaHCO₃ 25.0; Glucose 11.0; ascorbic acid 0.11. The bathing fluid, kept at 37.0±0.5°C, was saturated with a gas mixture of 95% O₂, 5% CO₂. The preparations were allowed to equilibrate for at least 1 h under a resting tension of

1.5g, which is optimal in inducing the maximum contraction. Tension was recorded by a physiograph (Ugo Basile).

Cumulative concentration-effect curves were constructed from the response of the tissue to noradrenaline, in the absence and presence of L-NAME (3 \times 10⁻⁴ M, inhibitor of NO synthase - NOS) (Sigma Chemical Co., St Louis, Missouri, USA).

In another series of experiments, cumulative concentration effect curves for acetylcholine (ACh) and sodium nitroprusside (SNP) (both drugs Sigma Chemical Co., St Louis, Missouri, USA) were examined in noradrenaline-precontracted intact aortic rings at concentration that induced 60–80%. Removal of endothelium abolished the response to ACh.

Contribution of intracellular and extracellular Ca²⁺ in the enhanced reactivity of the aortic rings to noradrenaline

To further analyze the relative contribution of the release of intracellular Ca²⁺ on the enhanced reactivity to noradrenaline, contractile response to this agonist was obtained in calcium-free medium. With this purpose, the normal Krebs' solution was replaced by a Ca²⁺-free solution. The rings were exposed to this solution for 1 min and then were stimulated with 10⁻⁷ and 10⁻⁶ M noradrenaline and the developed tension was recorded. In addition, the role of extracellular Ca²⁺ mobilization was investigated by CaCl₂-induced contraction in the presence of noradrenaline. Endothelium-denuded rings were first contracted with noradrenaline (0.1mM) to deplete the intracellular Ca²⁺ stores in Ca²⁺-free solution (approximately 90 min) containing EDTA (1 mM) and then rinsed in Ca²⁺-free solution (without EDTA) containing noradrenaline (0.1 mM) [23].

Statistical analysis

Blood pressure and nutritional, metabolic and endocrine profiles were expressed as means \pm standard deviation. Comparisons between groups were performed using the Student *t*-test for independent samples. The mean weekly body weight, the glucose profile and blood pressure of the groups were compared by ANOVA for repeated measures and post hoc Bonferroni-test.

The concentration of vasoactive agents producing a response that was 50% of the maximum (EC50) and maximal responses was calculated in each experiment. The EC50 values, presented as mean with 95% confidence intervals and maximum responses (g of tension), presented as mean \pm SEM were compared by ANOVA and post hoc Tukey-test.

The level of significance was considered to be 5%.

Results

Nutritional, metabolic and endocrine profiles of the animals

Table 1 shows nutritional, metabolic and endocrine profiles of rats. Obese rats ingested less food than control, however calorie intake, index of obesity and final body weights at the end of 15 weeks were higher in obese than control group. Moreover, blood pressure did not differ between control and obese groups at any time (Table 1). Glucose tolerance was lower in obese rats (Figure 1).

The plasma leptin (C = 3.32±0.21; Ob = 12.34±3.26* ng/dL, n = 8), glucose levels (C = 92.1±6.3; Ob = 122.0±10* mg/dL, n = 8) and insulin levels (C = 1.11±0.22; Ob = 2.92±0.55* ng/dL, n = 8), were significantly higher in obese compared to control group (*P< 0.05).

Vascular alterations

In the absence of L-NAME, the reactivity to noradrenaline of intact aorta was shown to be increased between high-fat and standard diet rats (Figure 3 and Table 2,3). The removal of the endothelium caused a leftward shift and raised maximal response of the noradrenaline aorta

Variables	Groups	
	C	Ob
FBW (g)	438 ± 49	482 ± 54*
FI (g/dia)	23.1 ± 1.9	21.2 ± 2.4
CI (kcal/dia)	68.7 ± 5.1	80.3 ± 7.8*
BWG (g)	299 ± 52	342 ± 58*
EF (g)	6.78 ± 2.54	11.2 ± 4.5*
RF (g)	7.25 ± 3.61	11.8 ± 5.1*
VF (g)	4.76 ± 2.98	8.61 ± 3.75*
TF (g)	18.8 ± 8.6	31.5 ± 12.8*
AI (%)	4.09 ± 1.48	6.45 ± 2.16*

Control rats received a standard diet (4% fat, 42.7% carbohydrate and 22% protein) and obese rats received a high-fat diet (20% fat, 26.4% carbohydrate and 20% protein) for 15 weeks. FBW - final body weight; FI - food intake; CI - calorie intake; EF - epididymal fat; RF - retroperitoneal fat; VF - visceral fat; TF - total fat; AI - adiposity index. Values are expressed as mean ± SD. *p < 0.05 vs control (Student t-test for independent samples). Number of animals: 8

Table 1: Effect of high-fat diet-induced obesity on the general characteristics of rats.

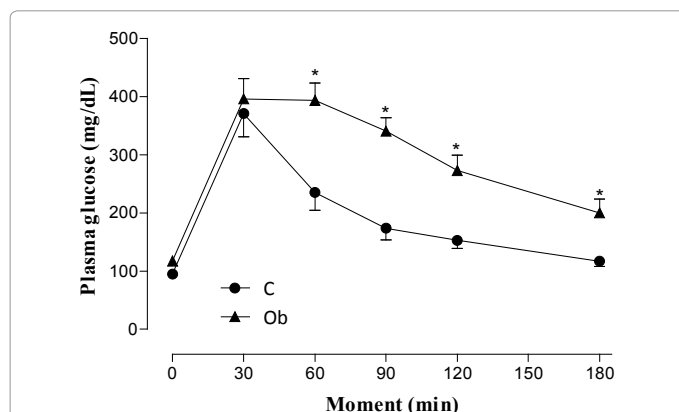


Figure 1: Glucose tolerance test in control, receiving a standard diet: 4% fat, 42.7% carbohydrate and 22% protein, for 15 weeks (n = 16) and obese, submitted to 15 weeks of high-fat diet: 20% fat, 26.4% carbohydrate and 20% protein (n = 16) rats. Values are expressed as mean ± SEM. *P < 0.05 vs control group. ANOVA and Bonferroni test. Number of animals: 8.

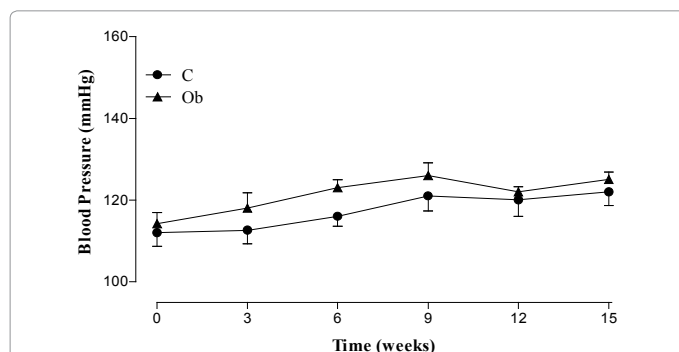


Figure 2: Development of blood pressure of control (C) rats received a standard diet (4% fat, 42.7% carbohydrate and 22% protein) and obese (Ob) rats received a high-fat diet (20% fat, 26.4% carbohydrate and 20% protein) for 15 weeks. Values are expressed as mean ± SEM. Number of animals: 8.

Agonist	Maximal response (g)		
	C	Ob	
Noradrenaline	+E	2.65 ± 0.21	1.82 ± 0.45*
	-E	4.58 ± 0.64†	4.10 ± 0.24†
Noradrenaline/L-NAME	+E	4.62 ± 0.70†	4.12 ± 0.40†
	-E	4.64 ± 0.55†	4.18 ± 0.25†

Control (C) rats received a standard diet (4% fat, 42.7% carbohydrate and 22% protein) and obese (Ob) rats received a high-fat diet (20% fat, 26.4% carbohydrate and 20% protein) for 15 weeks. Maximal response values are expressed as mean ± SEM. *P < 0.05 vs control group; †P < 0.05 vs aortic rings with endothelium in absence inhibitor. ANOVA and Tukey-test. Number of animals: 8

Table 2: Maximal response values (g) to noradrenaline obtained in two rings, one with and the other without endothelium. In presence of absence of L-NAME (3x10⁻⁴), of the same thoracic aorta from control and obese rats.

Agonist	EC50 (x10 ⁻⁷ M)		
	C	Ob	
Noradrenaline	+E	4.58 (3.27-6.42)	1.08 (0.55-2.17)
	-E	0.24 [†] (0.08-0.73)	0.16 [†] (0.07-0.38)
Noradrenaline/L-NAME	+E	0.89 [†] (0.22-3.53)	0.99 [†] (0.59-1.65)
	-E	0.36 [†] (0.28-3.92)	0.61 [†] (0.29-1.29)

Control (C) rats received a standard diet (4% fat, 42.7% carbohydrate and 22% protein) and obese (Ob) rats received a high-fat diet (20% fat, 26.4% carbohydrate and 20% protein) for 15 weeks. EC50 values are expressed as mean followed by 95% confidence interval in parenthesis. *P < 0.05 vs aortic rings with endothelium in absence inhibitor. ANOVA and Tukey-test. Number of animals: 8

Table 3: EC50 values to noradrenaline obtained in two rings, one with (+E) and the other without (-E) endothelium, in presence of absence of L-NAME (3x10⁻⁴), of the same thoracic aorta from control and obese rats.

Agonist	Relaxation		
	C	Ob	
Acetylcholine	Maximal response (%)	62.4 ± 8.63	82.6 ± 8.20*
	EC50% (10 ⁻⁶ M)	5.29 (0.58-48.3)	0.35 [†] (0.06-2.25)

Control (C) rats received a standard diet (4% fat, 42.7% carbohydrate and 22% protein) and obese (Ob) rats received a high-fat diet (20% fat, 26.4% carbohydrate and 20% protein) for 15 weeks. Maximal response and EC50 values are expressed as mean ± SEM and mean followed by 95% confidence interval in parenthesis, respectively. *P < 0.05 vs control group. ANOVA and Tukey-test. Number of animals: 8

Table 4: Maximal response and EC50% values to acetylcholine obtained in aortic rings with endothelium of the same thoracic aorta from control and obese rats.

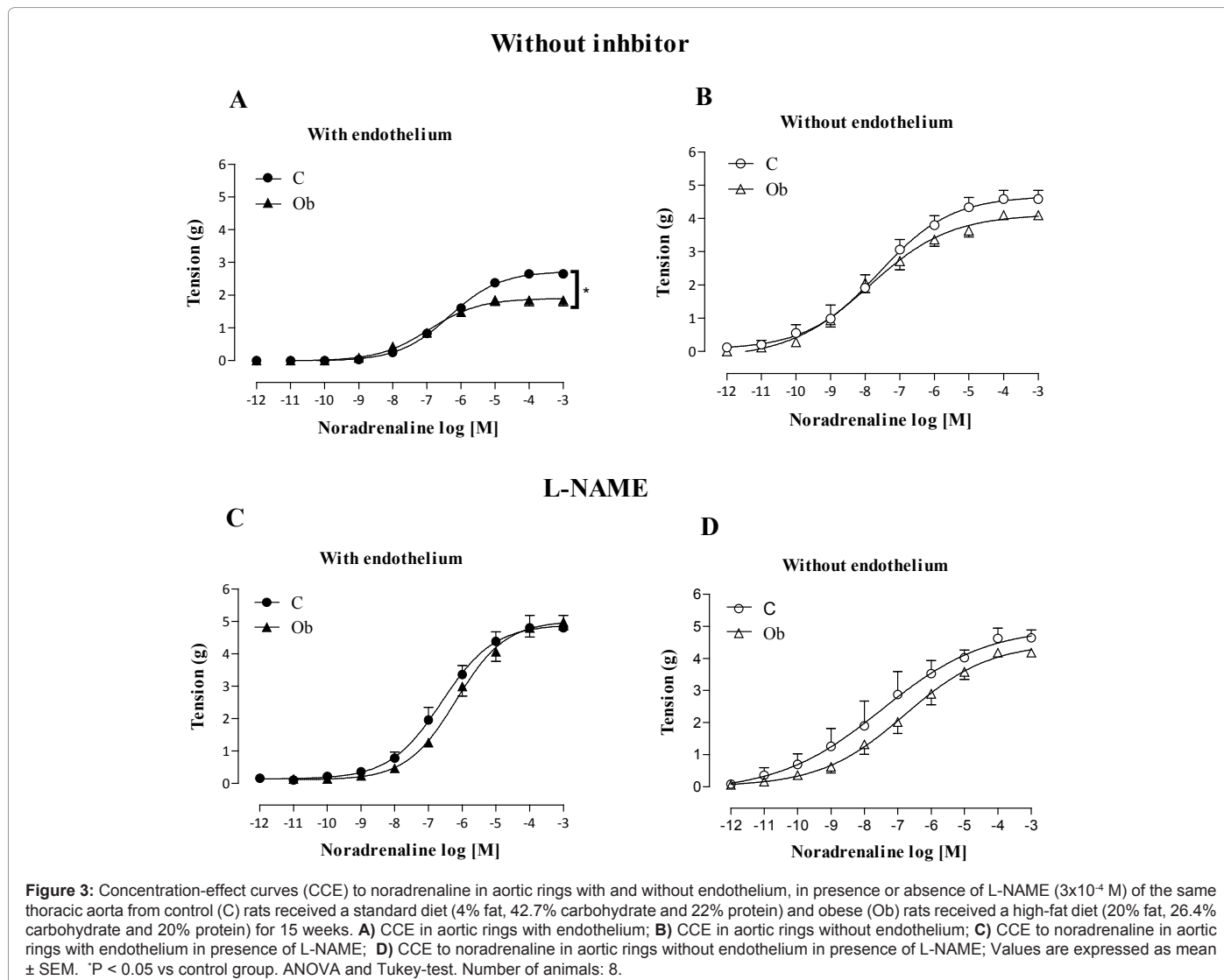
Agonist	Maximal response [relaxation (g)]		
	C	Ob	
Sodium Nitroprusside	+E	104 ± 5.4	104 ± 4.9
	-E	101 ± 5.4	100 ± 2.9

Control (C) rats received a standard diet (4% fat, 42.7% carbohydrate and 22% protein) and obese (Ob) rats received a high-fat diet (20% fat, 26.4% carbohydrate and 20% protein) for 15 weeks. Maximal response values are expressed as mean ± SEM. ANOVA and Tukey-test. Number of animals: 8

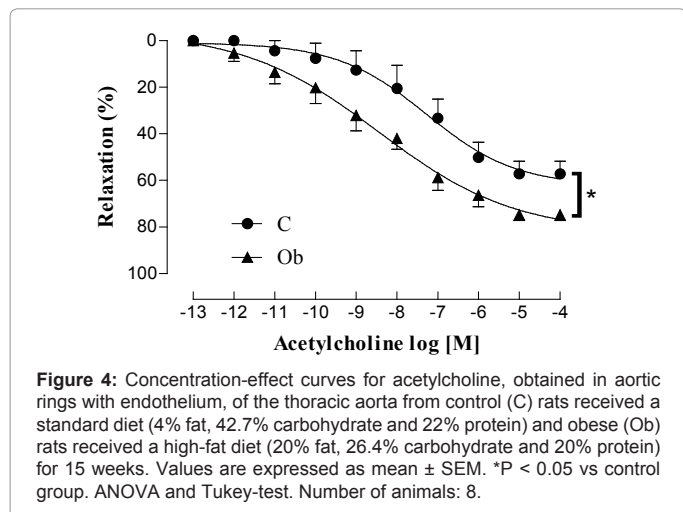
Table 5: Maximal response values (g) to sodium nitroprusside obtained in two rings, one with and the other without endothelium of the same thoracic aorta from control and obese rats.

curves that was similar in both controls and high-fat diet obese rats (Figure 3 and Table 3,4).

The presence of L-NAME produced a leftward shift and an increase in the aorta maximum response of the noradrenaline curves that was similar in intact aortas from high-fat diet obese than control rats (Figure 3 and Table 2,3).



Independently of L-NAME presence, the reactivity to noradrenaline did not differ among aortas without endothelium (Figure 3 and Table 2,3).



Agonist	EC50 ($\times 10^{-9}$ M)	
	C	Ob
Sodium Nitroprusside	+E	5.804 (2.02-16.6)
	-E	4.143 (2.53-0.76)

Control (C) rats received a standard diet (4% fat, 42.7% carbohydrate and 22% protein) and obese (Ob) rats received a high-fat diet (20% fat, 26.4% carbohydrate and 20% protein) for 15 weeks. EC50 values are expressed as mean followed by 95% confidence interval in parenthesis. ANOVA and Tukey-test. Number of animals: 8

Table 6: EC50 values to sodium nitroprusside obtained in two rings, one with (+E) and the other without (-E) endothelium of the same thoracic aorta from control and obese rats.

In aortic rings with endothelium of high-fat diet obese group, the acetylcholine determined increase of maximal response versus the control group and did not modify the EC50 value (Figure 4 and Table 4), the removal of endothelium abolished the relaxing of aortic rings (dates no shows). However, the sodium nitroprusside, did not change the maximal response and EC50 values between high-fat diet obese and control groups, in both aortic rings with and without endothelium (Figure 5 and Table 5,6).

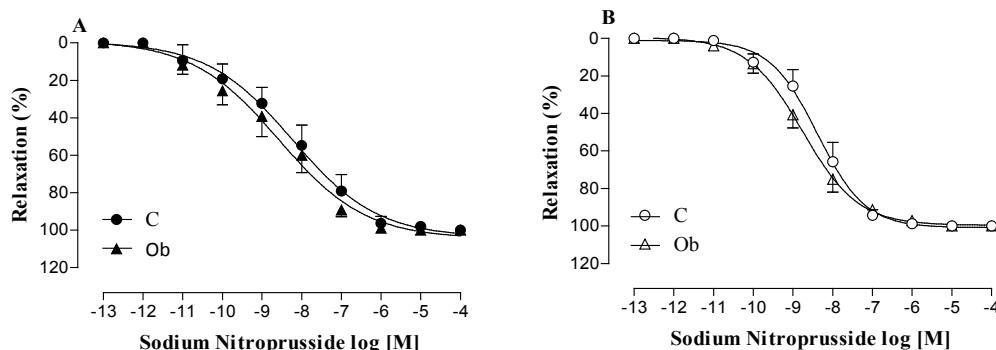


Figure 5: Concentration-effect curves (CCE) to sodium nitroprusside in aortic rings with and without endothelium of the same thoracic aorta from control (C) rats received a standard diet (4% fat, 42.7% carbohydrate and 22% protein) and obese (Ob) rats received a high-fat diet (20% fat, 26.4% carbohydrate and 20% protein) for 15 weeks. **A)** CCE in aortic rings with endothelium; **B)** CCE in aortic rings without endothelium. Values are expressed as mean \pm SEM. Number of animals: 8.

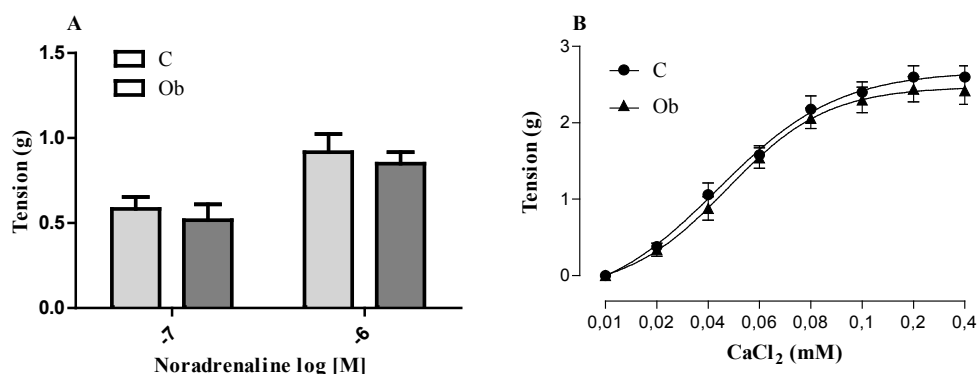


Figure 6: Data were obtained in aortic rings without endothelium of the thoracic aorta from control (C) rats received a standard diet (4% fat, 42.7% carbohydrate and 22% protein) and obese (Ob) rats received a high-fat diet (20% fat, 26.4% carbohydrate and 20% protein) for 15 weeks. **A)** Measurement of tension in cytosolic-free Ca^{2+} induced by noradrenaline (10^{-7} and 10^{-6} M) were measured in in aortic rings without endothelium; **B)** Concentration-effect curves to CaCl_2 in aortic rings without endothelium determined in Ca^{2+} -free solution containing noradrenaline ($0.1\mu\text{M}$). Values are expressed as mean \pm SEM. Number of animals: 8.

There was no statistic difference between high-fat diet obese and standard group to maximal response to NA in absence of $[\text{Ca}^{2+}]_i$ [maximal response (g/tension): C 0.58 ± 0.07 to NA 10^{-7} M and 0.91 ± 0.10 to NA 10^{-6} ; Ob 0.52 ± 0.11 to NA 10^{-7} M and 0.84 ± 0.08 to NA 10^{-6} M] (Figure 6). This experiment was performed in rings without endothelium.

In addition, no significant change in the maximal response and in the EC50 values was observed to CCE to CaCl_2 [maximal response (g/tension): C: 2.68 ± 0.40 and Ob: 2.47 ± 0.27 ; EC50 (M): C: 1.53 (0.30-7.76) and Ob: 2.32 (0.64-8.36)] (Figure 6). This experiment was performed in rings without endothelium.

Discussion

In this present research, high-fat diet rats developed obesity characterized by increase in final body weight and fat-pad mass. Although the obese group has ingested less food, the higher weight gain exhibited by these animals was most likely due to the increased calorie intake and feed efficiency related to control. Besides, the obese rats developed metabolic disorder such as glucose intolerance, hyperinsulinemia and hyperleptinemia, characteristics frequently related to human obesity [20,24,25].

The vascular dysfunction is link to diet-induced obesity has been related for several authors [21,26,27]. In the present study, the obesity determined adaptive vascular responses; one of response

was characterized for hyporeactivity to noradrenaline. Fatani et al. [21] observed similarly findings to of present research. Moreover, the presence of L-NAME abolished the hyporeactivity observed to noradrenaline, this date suggest the involvement of NO pathway;

Contrarily, the literature reports impair of pathway NO in the obesity [28]. The variance among these findings might be related to obesity model. Currently, any obesity models have been used, such as: genetics and different models of diet [29-31]. However, previous study of our laboratory showed similarly behavior related with pathway l-arginine/NO in aortas of rats exposed to same diet for 30 weeks, since that L-NAME pre-incubated in CCEs to noradrenaline produced a leftward shift of the diet-induced obesity [32].

Several mediators are able of stimuli to releasing of NO through endothelial nitric oxide synthase (eNOS), such as: insulin [33], leptin [34], glucocorticoid [35] among others. The activation of guanylate cyclase and the subsequent accumulation of cGMP are the main mechanisms of NO-induced vasodilatation [36]. Thus, hyperinsulinemia and hyperleptinemia could be an explanation to decreased response to noradrenaline which was observed in the present research.

In addition, the adaptive vascular response was dependent of endothelial integrity, since the removal of endothelium abolished this response.

Another finding our research was that vascular response produced by obesity proved to be nonspecific to noradrenaline. Since, acetylcholine also produced changes in aortas of obese rats, these alterations was characterized by decrease of EC50 value and increase of maximal response when compared with lean rats. In addition, these results further reinforce the involvement of pathway l-arginine/NO, whereas the acetylcholine is an agonist able to stimuli the releasing of NO [37]. However, several studies show damage of hypercaloric diet on the vascular reactivity to vasodilatation agents. For example, the diet-induced obesity for hypercaloric diet led an injury of endothelium-dependent relaxation [26,27]. The divergence of results might be due to different composition or time of exposition to diet, as previously observed for Mundy et al. [27]. The authors reported a damage of endothelial function only in the high fat, but no in moderate fat diet.

The sodium nitroprusside is an endothelium-independent vasodilator capable of inducing vasodilation by providing an inorganic source of NO [38]. Differently of acetylcholine, the sodium nitroprusside did not change, in both parameters maximal response and EC50, the vascular response of obese rats; these results corroborate the findings (2004) [39], who also did not observed alterations in mesenteric arteries with this agonist endothelium-independent vasodilator.

With aim of examine whether changes in Ca²⁺ mobilization could be involved in the adaptive vascular response produced by obesity, we investigated the vascular response to noradrenaline and of CaCl₂ in Krebs-Henseleit Ca²⁺ free solution, these parameters allow infer about the intracellular stores and influx of extracellular Ca²⁺ ions, respectively. Since there are no changes to noradrenaline and to CaCl₂ response were observed in this condition, the results suggests that adaptive vascular response induced by obesity is not involved with alterations of Ca²⁺ flux.

In conclusion, our results can help to understand paradox obesity, whereas we observed decreased maximal response to noradrenaline and increase of maximal response to acetylcholine, as well as, rise of NO pathway in aortic rings of obese rats. These dates together could be considered as beneficial vascular response; thus the vascular responses observed in present work might have occurred with the aim of decrease of cardiovascular risk linked with obesity pathology. In addition, the absence of hypertension arterial would be explained for improve of vascular response observed in diet-induced obesity.

Acknowledgements

Research supported by FAPESP (2009/03771-2).

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This article was originally published in a special issue, **Cardiovascular and Immunological Diseases** handled by Editor(s). Dr. Włodzimierz Luczynski, Medical University of Białystok, Poland

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