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Letter to the Editor

Cardiac programming in rats submitted to leptin treatment during lactation

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Experimental studies have shown that hormones and nutrition status, which affect development during sensitive periods early in life, permanently program the structure and function of body tissues and systems [1,2]. Malnutrition in lactating rats could program changes in leptin action and theoretically affect metabolic rate, changing leptin serum concentration of the mothers and of their pups [2]. Hyperleptinemia in both the first and the last 10 days of lactation was associated with a higher serum leptin concentration at 150 days of age and, paradoxically, with a higher food intake and body weight, showing resistance to the anorectic effect of leptin [1], as observed for those animals programmed by maternal malnutrition during lactation [2] but the effects were more marked when the leptin was injected within the first 10 days. It was observed that leptin treatment during the first 10 days of lactation has a long-term effect on adrenal medullary function by increasing catecholamine synthesis and secretion, suggesting a selective leptin resistance in this experimental model and that this overstimulated sympathoadrenal system could contribute to the development of adult chronic diseases [3]. So the aim of the present work was to study if leptin treatment of the pups during the first 10 days of lactation, which may mimic maternal malnutrition during this period, programs cardiovascular function and may be involved in development of chronic diseases.

This study was performed at the Laboratory of Experimental Pharmacology of Fluminense Federal University and approved by local Ethics Committee (CEPA/UFF00123-09). Wistar rats were treated with leptin (PeproTech Inc., London, UK) at a dose of 8 mg/100 g body weight daily for the first 10 days of lactation or saline (Control — Leptin naïve) as previously described [1,3].

Anthropometrical parameters such as abdominal circumference (AC)/thoracic circumference (TC) ratio and body mass index (BMI) were determined in all rats at 30 and 150 days of age [4].

Functional assays were performed with animals at the same age. Systolic blood pressure (SBP) was obtained using tail-cuff method [5]. All electrocardiographic recordings were conducted in awake rats on derivation DI: heart rate (HR; beats per minute), RR interval (s), QRS complex (s), PR interval (s) and QT interval (s) [6]. The relationship between the QT interval and RR interval was individually assessed to obtain physiologically relevant values for the heart rate-corrected QT interval (QTc): QT / √RR [6]. Echocardiography was performed with anesthetized rats according to the American Society of Echocardiography [7], being acquired: left ventricle ejection fraction (LVEF); intraventricular septum thickness (IVS); left ventricle posterior wall thickness (LVPW); left ventricle internal diameter (LVID); relative wall thickness (RWT); left ventricle mass (LV mass) and left-atrium-to-aorta ratio (LA/Ao ratio), in systole and/or in diastole. Mitral deceleration time (Mitral DT) was measured using Echo Doppler. Rats were also subjected to a treadmill exercise test to achieve their maximal effort (distance performed, time spent and speed developed) addressed when rats were unable to run voluntarily after strenuous exercise [7].

All data are expressed as mean ± SEM. A two-tailed unpaired Student's t-test was performed and statistical significance was accepted at the 0.05 level (Graph-Pad Prism 5.0).

Table 1 shows that 30 and 150 day-old rats treated with leptin during lactation present higher AC/TC ratio and BMI compared to their respective controls. Although this ratio is not an accurate as marker of increased body weight and obesity in rats, there is a positive correlation between BMI with carcass fat, being obesity easily estimated from this anthropometrical parameter in rats [4]. A positive correlation between BMI with serum triacylglycerol, dyslipidemic profile and oxidative

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Table 1
Anthropometrical and functional (hemodynamic, echocardiography and electrocardiography) data obtained from rats that received saline (Control — Leptin naive) or leptin (Leptin) during lactation at 30 and 150 days of age.

Variables	30 days of age		150 days of age	
	Control	Leptin	Control	Leptin
	n = 10	n = 11	n = 11	n = 15
AC/TC	1.126 ± 0.010	1.174 ± 0.013*	1.115 ± 0.008	1.145 ± 0.011*
BMI (g/cm^2)	0.460 ± 0.008	0.482 ± 0.006*	0.746 ± 0.006	0.784 ± 0.010*
	n = 10	n = 12	n = 8	n = 12
SBP (mm Hg)	118.3 ± 0.3	118.8 ± 0.5	118.6 ± 0.6	118.9 ± 0.4
	n = 12	n = 12	n = 11	n = 15
LVEF (%)	93.83 ± 0.87	91.77 ± 1.18	88.06 ± 1.65	81.32 ± 2.29*
LA/Ao ratio	1.020 ± 0.006	1.048 ± 0.011*	1.020 ± 0.017	1.256 ± 0.046*
IVSd (cm)	0.133 ± 0.003	0.144 ± 0.004*	0.206 ± 0.005	0.203 ± 0.007
IVSs (cm)	0.220 ± 0.008	0.233 ± 0.008	0.339 ± 0.011	0.318 ± 0.011
LVPWd (cm)	0.136 ± 0.003	0.149 ± 0.005*	0.215 ± 0.007	0.212 ± 0.007
LVPWs (cm)	0.226 ± 0.008	0.236 ± 0.009	0.325 ± 0.009	0.317 ± 0.009
LVIDd (cm)	0.390 ± 0.013	0.384 ± 0.018	0.681 ± 0.020	0.763 ± 0.028*
LVIDs (cm)	0.138 ± 0.004	0.153 ± 0.007	0.297 ± 0.019	0.376 ± 0.025*
RWT (cm)	0.704 ± 0.014	0.787 ± 0.032*	0.623 ± 0.023	0.566 ± 0.031
LV mass (g)	0.775 ± 0.011	0.833 ± 0.025*	1.44 ± 0.04	1.65 ± 0.08*
Mitral DT (ms)	61.67 ± 2.21	66.67 ± 2.43	85.82 ± 3.19	77.47 ± 2.39*
	n = 8	n = 9	n = 5	n = 9
HR (BPM)	410.2 ± 5.9	414.8 ± 11.7	376.6 ± 3.3	438.2 ± 9.8*
RR (s)	0.142 ± 0.005	0.142 ± 0.005	0.156 ± 0.003	0.137 ± 0.003*
QRS (s)	0.0162 ± 0.0002	0.0161 ± 0.0002	0.0126 ± 0.0014	0.0146 ± 0.0003
PR (s)	0.045 ± 0.001	0.045 ± 0.001	0.046 ± 0.001	0.046 ± 0.001
QT (s)	0.053 ± 0.002	0.053 ± 0.002	0.047 ± 0.005	0.054 ± 0.004
QTc (s)	0.141 ± 0.006	0.142 ± 0.005	0.120 ± 0.014	0.145 ± 0.013

AC/TC — abdominal circumference/thoracic circumference ratio; BMI — body mass index; SBP — systolic blood pressure; LVEF — left ventricle ejection fraction; LA/Ao ratio — left-atrium-to-aorta ratio; IVS — intraventricular septum thickness; LVPW — left ventricle posterior wall thickness; LVID — left ventricle internal diameter; RWT — relative wall thickness; LV mass — left ventricle mass; Mitral DT — mitral deceleration time; d — diastole; s — systole; HR — heart rate.
* $P < 0.05$ — Leptin vs Control.

stress in serum is also described [4]. So, cardiometabolic risk is raise in rats submitted to neonatal leptin treatment.

Although SBP are not different between rats that received saline or leptin during lactation, data from echocardiographic studies (Table 1) show that LA/Ao ratio and LV mass are raise in rats treated with leptin during lactation. The observed left atrium enlargement is considered useful as a quick bedside technique to screen for cardiac disease [8]. Increased LV mass can be related to either concentric or eccentric hypertrophy, depending on the RWT. So 30 day-old rats treated with leptin during lactation presents a concentric hypertrophy while 150 day-old rats of the same group presents an eccentric hypertrophy. These data are suggestive of cardiac dysfunction [7].

The abnormality of the left ventricle geometry observed in young rats treated with leptin is related to an increase of IVS and LVPW in diastole while the abnormality of the left ventricle geometry observed in adult rats treated with leptin is related to an increase of LVID [7].

LVEF and Mitral DT were diminished in the older rats treated with leptin compared to control (Table 1). Although diastolic dysfunction is not uncommon in patients with normal wall thickness, left ventricular hypertrophy is among the important reasons for it. In patients with diastolic heart failure, concentric hypertrophy (as seen in young rats treated with leptin) can be observed. In contrast, eccentric hypertrophy is usually present in patients with depressed LVEF that also present normal blood pressure (as seen in adult rats treated with leptin). In addition, patients with impaired left ventricle relaxation filling are the least symptomatic, while a short Mitral DT, as seen in 150 day-old rats, characterizes advanced diastolic dysfunction, increased LA pressure and worse functional class. A restrictive filling pattern is associated with a poor prognosis, especially if it persists after preload reduction [9].

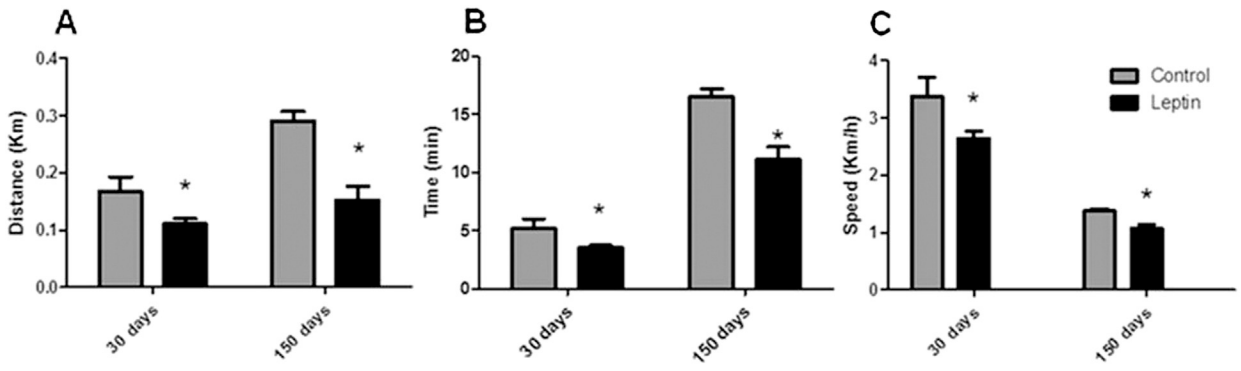


Fig. 1. (A) Distance preformed, (B) time spent and (C) speed developed by rats that received saline (Control — Leptin na ve — gray bars) or leptin (Leptin — black bars) during location at 30 (n = 11–15) and 150 days (n = 5) of age. *P < 0.5.

Data from electrocardiographic studies show that HR was elevated and RR interval diminished in adult rats submitted to leptin treatment, suggesting the raise of sympathetic activity. Our data support the idea that imprinting factors which increase leptin and catecholamine levels during the neonatal period could be involved in development of adult chronic diseases [3].

Fig. 1 shows that distance performed, time spent and speed developed were lower both in young and adult rats treated with leptin. This data show that cardio-respiratory capacity is diminished in these rats [7].

Thus, our data suggest that the signs of cardiac dysfunction displayed by our experimental model in youth is compatible with diastolic heart failure (stage B), evolving to systolic dysfunction in adulthood [7,9,10].

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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