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MATERNAL FOOD RESTRICTION DURING LACTATION LEADS TO SEX-SPECIFIC BLOOD HYPERTENSION AND CARDIAC REMODELING IN THE OFFSPRING

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Abstract

Dietary restriction during pregnancy and puberty is a risk factor to hypertension onset at adulthood. The aim of this study was to evaluate the effect of maternal malnutrition during lactation on cardiovascular parameters, in both sexes of rat pups at 120-day-old. Maternal food restriction lead to arterial hypertension, baroreflex impairment, cardiac remodeling and increased collagen deposition in the aorta, in adult male offspring. The females did not show functional or morphological disruptions. Together, these results show that maternal food restriction during lactation promotes cardiometabolic programming, generating cardiovascular alterations in male adult rat offspring, however female offspring present some kind of cardioprotective effect.

Keywords: Food Restriction, Hypertension, Cardiac Remodeling

1. Introduction

The onset of diseases at adulthood may be associated with conditions to which the individual was exposed in the early life stages. The lactation is a stage of extreme importance as it is the main source of nutrients for the offspring. Recent studies related that restrictive diets early in life can impact in the cardiovascular health later in life. The present study aims to evaluate the effects of maternal food restriction during the lactation on the cardiovascular parameters of adult Wistar rat offspring.

2. Material and methods

Pregnant Wistar rats (n=10) were separated into two groups: control group (CO), mothers received daily standard chow *ad libitum*; and FR group, mothers fed daily 50% of standard chow intake by CO mothers. The intervention was carried out from the first postnatal day (PND1) to the PND14 (2/3 of lactation), after the PND14 all mothers received standard chow *ad libitum*. The protocols were approved by the CEUA / UFG (process n. 023/2015). At weaning, male and female offspring were monitored until PND120. Cardiovascular parameters, heart rate, mean arterial pressure (MAP) and baroreflex index were assessed in conscient animals through previously implanted catheters. Heart and thoracic aorta were dissected after the euthanasia and fixed for histological analysis.

All data are expressed as Mean ± Standard Error of Mean (SEM). To analyze the differences between the groups in relation to time, the *student's t test* analysis was used. For the statistical analysis and graphical production of the results, the *Prism* software (v9; GraphPad, San Diego, CA, USA) was used.

3. Results and discussion

At PND120, we observed an increase in mean arterial pressure in FR male rats (CO 107.2 ± 1.37 mmHg *vs* FR 136.6 ± 6.79 mmHg; $p<0.0003$), in systolic blood pressure (CO 133 .1 ± 2.55 mmHg *vs* FR 170.9 ± 9.89 mmHg; $p <0.0026$), diastolic blood pressure (CO 92.74 ± 1.65 mmHg *vs* FR 119.5 ± 5.33 mmHg; $p<0.0003$), but no change heart rate (CO 356.9 ± 9.19 bpm *vs* FR; 363 ± 7.70 bpm; $p<0.6165$). In addition, we observed a reduction in the baroreflex after injection of phenylephrine (CO -1.81 ± 0.22 Δbpm/ΔmmHg *vs* FR -1.18 ± 0.16 Δbpm/ΔmmHg; $p<0.0409$) and sodium nitroprusside injection (CO -4.81 ± 0.52 Δbpm/ΔmmHg *vs* FR -2.17 ± 0.21 Δbpm/ΔmmHg; $p<0.0002$) in male offspring. On the other hand, there was no significant change in these parameters in the female offspring. It is known that intrauterine protein malnutrition promotes an increase in systolic blood pressure in pups aged 4 weeks after weaning, this phenomenon was observed in both male and female (6). The 30% food restriction during the intrauterine phase was also able to increase the SBP, the blood insulin and leptin levels in the offspring at 100 days of age (7). It is known that hypertensive human and animals

have reduced baroreflex sensitivity due to autonomic dysfunction, with sympathovagal imbalance in relation to sympathetic hyperactivity (5). In the genesis of cardiovascular pathologies, such as hypertension and cardiac hypertrophy, an increase in sympathetic activity and circulating levels of catecholamines is observed (2). Hypertension onset can be a consequence generated by malnutrition, caused by increased sympathetic activity or endothelial dysfunction (1). It is known that endothelial alteration is a characteristic associated with fetal malnutrition, which is associated with insulin resistance and developing hypertension (4).

Due to pressure overload, FR male offspring showed cardiomyocyte hypertrophy (CO 10.75 ± 0.12 μm *vs* FR 12.66 ± 0.15 μm; $p<0.0001$), increased perivascular fibrosis (CO 2.69 ± 0.31 a.u. *vs* FR 4.25 ± 0.46 a.u.; $p<0.0141$) and increased interstitial fibrosis (CO 8.83 ± 0.82 % *vs* FR 12.92 ± 1.33 %; $p<0.0213$), indicating cardiac remodeling. On the other hand, female offspring did not show any morphological alterations. Increased collagen deposition causes disruption in myocardial architecture, promotes chamber rigidity in the left ventricle, and promotes impairment of cardiac function, causing signal conduction abnormalities and ventricular and atrial systolic and diastolic dysfunction (3).

One mechanism involved in the development of hypertension is the oxidative stress dependent vascular dysfunction DHE and DCF fluorescent probes were used to assess oxidative stress in the aorta, but no change was observed between in both groups and sexes.

4. Conclusion

Our results shown that maternal food restriction during lactation promotes sex-specific functional changes in the heart, cardiac remodeling and increased collagen deposition in the aorta, independent of the increase in oxidative stress. Considering that these cardiovascular effects appeared only in male offspring, we reinforce the idea that estrogens hormones are likely to protect female offspring from these damages.

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