Structural and functional changes in the left ventricle from rats that received a high-fat diet: influence of Ang II⇒AT_1R axis antagonism by Angiotensin-(3–4)

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Introduction: Obesity is a great pandemic of the 21st century that affects several countries worldwide with a marked worsening associated with comorbidities such as hypertension and dyslipidemia. Its impact on the cardiovascular system, including vessels and the heart, is associated with high mortality rates. The increasing use of the so-called "Western diets," with their high fat and Na+ contents, compromises organs and systems in overweight and obese people.
Methodology. Male Wistar rats received a high-lipid (HL) diet (70% of calories from fat) with a high NaCl content (40% higher than in control diets) for 106 days, from the 58th day of life. In parallel, another group received a control diet (CTR). We evaluated body mass (BM) and systolic blood pressure (SBP) over the entire period. At 104 days of exposure to the diets, the rats were individualized in metabolic cages. They received vehicle (water) or Ang-(3–4) (4 doses of 80 mg/BM), the shortest active peptide of the renin-angiotensin-aldosterone system (RAAS), which antagonizes the effects of Ang II in different pathophysiological conditions. Over the next two days, echographic studies in heart and liver and electrocardiographic recordings were performed. On day 106, the rats were euthanized. The Committee for Ethical Use of Animals at UFRJ (#075/19) approved the study.
Results. HL rats developed significant overweight (~10%) and hypertension (143±0.5 mmHg *vs*. 131±0.7 mmHg in CTR, $P<0.0001$), which was reversed by Ang-(3–4) administration (131±0.7 mmHg). Echocardiographic records showed increased left ventricle diameter in systole (~15%, $P<0.0001$) associated with a decrease in the shortening fraction (~10%, $P<0.0001$), both reversed by Ang-(3–4) administration. The increase in end-systolic volume found in HL rats was also reversed by Ang-(3–4) ($P=0.0068$). Ejection fraction and stroke volume did not change with HL diet. Liver ultrasonography images from HL rats revealed marked signs of steatosis (85% compared to CTR rats) reversed by Ang-(3–4). Furthermore, HL rats revealed atypical dyslipidemia: (1) decreased plasma triglycerides (~65%), (2) decreased high-density lipoproteins (~50%), and (3) increased low-density lipoproteins (~60%), without modifications in total cholesterol. The electrocardiogram showed no differences in HL rats.
Conclusions. The HL rats revealed an early myocardial remodeling in the left ventricle that indicates a possible future development of heart failure. The Ang-(3–4) effects indicate that overweight, visceral fat dysfunction, and hypertension have the Ang II ⇒ AT_1R axis as a crucial etiopathogenic factor. Atypical dyslipidemia associated with changes in proximal renal tubules (Luzes *et al*., Biochim Biophys Acta Mol Basis Dis

1867: 166012, 2021) allows us to conclude that obesity and hypertension resulting from prolonged fat and salt ingestion can lead to the establishment of a hepatocardiorenal syndrome.

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