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Micro computed tomography detects changes in liver density in control and in prediabetes rats

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Abstract

Fatty liver disease is an early event in the development of insulin resistance that predicts the presence and progression of the metabolic syndrome. In humans, fatty liver diagnosis is usually performed by imaging techniques based on ultrasound, computed tomography and magnetic resonance. Rodent models are often used in metabolic research allowing access to tissue biopsies however, studies describing *ex vivo* computed tomography of biological samples are scarce. X-ray Micro Computed Tomography (Micro-CT) is an imaging technique that reveals the internal structure of materials in great detail, also allowing a quantitative analysis of properties such as density measured as arbitrary Hounsfield Units (HU). Herein, we tested the hypothesis that Micro-CT detects changes in liver tomographic density induced by metabolic diseases and its reversal upon therapeutic surgical intervention. Two groups of male Wistar rats were used: a group submitted to a hypercaloric diet for 14 weeks to induce prediabetes and the control group submitted to a standard diet). The animals were randomly submitted to a surgical treatment and maintained on their respective diets after the procedure for 11 more weeks. Liver and adipose tissues samples were excised and samples were scanned using a compact X-ray micro-CT scanner. The projection images obtained were analyzed and reconstructed and values of HU density were calculated after calibration for all samples. Results showed that liver density was lower in prediabetes rats (74.8±5.87 HU) than in control animals (97.2±6.3 HU), $p<0.05$. Liver density was not affected by surgical treatment in control animals however, in prediabetes animals, the surgical therapy restored liver density to control values. Visceral fat density was significantly lower than hepatic density, as expected and was affected, neither by the disease condition nor by the surgical treatment. We concluded that micro-CT detects metabolic disease-induced changes in liver density, but not in visceral adipose tissue density in biopsy samples ex vivo. Changes in hepatic density, assessed by micro-CT, correlate with disease state and with therapeutic interventions.

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1. Introduction

As recently reported by the World Health Organization's World Health Statistics 2014 chronic non-communicable diseases, such as cardiovascular and metabolic diseases contribute significantly to mortality and morbidity in the world without significant advances in the field of therapeutics [1,2]. While investigating pathophysiological mechanisms of insulin-resistance associated conditions, our team unraveled an innovative role for a peripheral nerve, the carotid sinus nerve (CSN), in the pathogenesis of insulin resistance and dysglycemia. The therapeutic potential of this finding was demonstrated by prevention of metabolic disease progression achieved by CSN surgical resection in animal models of prediabetes [3]. The CSN is the sensitive nerve that connects the peripheral chemoreceptors, located at the carotid bodies (CB), with the central nervous system. These tiny organs are located bilaterally in the bifurcation of the common carotid arteries and respond to low oxygen levels in the blood by increasing chemosensory activity in the CSN to signal the sympathetic nervous system to increase ventilation and cardiac output [4, 5]. Besides its role in the control of ventilation, the CB has been proposed as a metabolic sensor, implicated in the control of energy homeostasis [3,6-9], playing a direct role in the etiology of insulin resistance, the core metabolic feature of the metabolic syndrome and type 2 diabetes [3, 6, 8-11] (Fig.1).

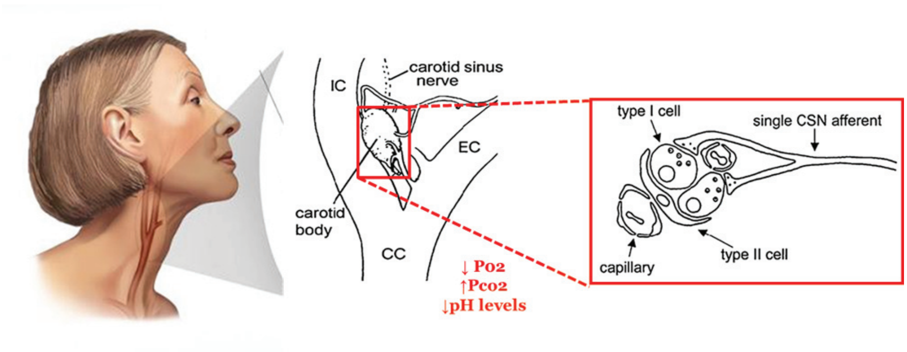

Fig. 1. The carotid bodies (CB) are peripheral chemoreceptors that sense changes in arterial blood O_2, CO_2 and pH levels. Hypoxia, hypercapnia and acidosis activate the CB, which respond by increasing the action potential frequency in their sensory nerve, the carotid sinus nerve (CSN). CSN activity is integrated in the brain stem to induce a panoply fan of cardiorespiratory reflexes aimed, primarily, aimed to normalize the altered blood gases, via hyperventilation, and to regulate blood pressure and cardiac performance, via sympathetic nervous system activation. Besides its role in the cardiorespiratory control, in the last decade the CB has been proposed as a metabolic sensor implicated in the control of energy homeostasis and, more recently, in the regulation of whole body insulin sensitivity. CC- common carotid artery; IC-internal carotid artery; EC- external carotid artery; CSN: carotid sinus nerve; type I cell: chemosensory glomus cell; type 2 cell: sustentacular glomus cell. Adapted with permission from Gonzalez et al., 2011 Respiratory Physiology & Neurobiology and Creative Commons License.

Knowing that fatty liver disease is an early event in the development of insulin resistance that predicts the presence and the progression of the metabolic syndrome [12], the work presented herein had two main aims: the first one was to test if X-ray Micro Computed Tomography (Micro-CT) could detect changes in liver and visceral adipose tissue ex vivo biopsy samples of control and metabolic syndrome rats; the second aim was to evaluate if the surgical resection