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Mitochondrial metabolism and morphology in a rat model of NAFLD

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NAFLD (non-alcoholic fatty liver disease) is a condition, characterized by fatty liver, that, if untreated, can progress to NASH (non-alcoholic steatohepatitis) and, finally, to cirrhosis. Mitochondrial dysfunction is a crucial element for the progression of NAFLD to NASH. Our objective was studying both morphological and physiological mitochondrial alterations in a rat model of NAFLD and NASH. Sprague Dawley rats were fed either by a standard diet (35% of energy from fat) or by a high fat diet (HFD) (71% of energy from fat). Diets were given ad libitum for a maximum of four weeks and then rats were killed by decapitation after 1, 2, 3, and 4 weeks. A portion of liver samples was processed for light and transmission electron microscopy (TEM) for steatosis assessment, a part for high resolution scanning electron microscopy (HRSEM) to evaluate 3D mitochondria morphology, the remaining part for oxidative phosphorylation experiments (OXPHOS). Measurements of OXPHOS were performed on freshly isolated mitochondria in a Clark-type oxygen electrode. Several substrates were added to mitochondria to test the efficiency of electron transport chain complexes (ETC) and to test the efficiency of several enzymes involved in fatty acid oxidation (FAO). At three and four weeks of HFD, signs of hepatic steatosis were evident (as an increased amount of intracellular lipid droplets) on histological sections and TEM images. OXPHOS measurements indicated that, compared to controls, in the first week, HFD rats had an increased oxygen consumption with each substrate, in the second, third and fourth week OXPHOS efficiency had a tendency to decline with substrates inherent to glycolitic metabolism, but it was higher with substrates stimulating FAO. There were not notable differences in Respiratory Control Ratio and ADP/O ratio between HFD and controls, proving that the integrity of mitochondria was preserved and coupled to phosphorylation. HRSEM observations indicated that variations on inner mitochondrial morphology in HFD rats, appeared in the third and fourth week, when mitochondrial cristae were less, and cristal shape was often lamellar rather than tubular. Concluding, following HFD mitochondria exhibited first an increase in oxidative metabolism (with normal ultrastructural morphology) and later an alteration in the oxidative phosphorylation apparatus associated to mitochondrial cristae injury. These preliminary results suggest that in order to develop a consistent mitochondrial impairment associated to NASH is necessary to extend HFD treatment for longer.

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Keywords: mitochondria, NAFLD, OXPHOS