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ORIGINAL ARTICLE

Aerobic physical training after weaning improves liver histological and metabolic characteristics of diet-induced obese rats

L'activité physique après le sevrage améliore l'étude histologique du foie et métaboliques caractéristiques des rats obèses induites par l'alimentation

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KEYWORDS
Liver;
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Steatosis

Summary
Objectives. — To evaluate liver mitochondrial function and its impacts on fat liver accumulation and the effects of the physical training in cafeteria diet feeding rats.
Methods. — Control (C), sedentary cafeteria diet rats (DIO), and trained cafeteria diet rats (TDIO) accompanied from 21 days old to 120 days old were submitted to body weight and adiposity analysis, glycemic and lipid profile, liver histology, liver mitochondrial analysis (lipid oxidation and phosphorylation capacity).
Results. — DIO presented elevated body weight and adiposity, and aerobic training (TDIO) improved these parameters. TDIO showed reduced triglycerides and LDL-cholesterol and elevated HDL-cholesterol. DIO presented higher fat liver accumulation that was reversed in TDIO. Liver mitochondria from DIO exhibited a higher β-oxidation capacity and an increase in the capacity of oxidizing succinate, with little effects of physical exercise. Our results demonstrated that in DIO, the development of steatosis preceded the establishment of body insulin resistance, which, in turn, has been considered the ''first hit'' in hepatic steatosis development. These suggest that some intrahepatic events could arise very early in conditions of poor nutrition and probably contribute to the development of NAFLD. Then, our results suggest that starting physical activity just after weaning decreased adverse effects of cafeteria diet on body composition, lipid profile, and liver fat deposition.

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MOTS CLÉS
Foie ;
Mitochondrie ;
Activité physique ;
Régime cafétéria ;
Stéatose

Résumé
Objectifs. — Évaluer l'intérêt de l'activité physique chez des rats nourris au régime cafétéria sur la fonction mitochondriale hépatique et l'accumulation de graisse dans le foie.
Méthodes. — Des rats témoins (C), sédentaires avec régime cafétéria (DIO), ou entraînés avec régime cafétéria (TDIO), ont été suivis du j21 au j120 après leur naissance. Le poids corporel et l'adiposité ont été mesurés, ainsi que les profils lipidique et glycémique. L'étude histologique du foie et la fonction de mitochondries hépatiques ont complété l'expérimentation (oxydation lipidique et capacité de phosphorylation).
Résultats. — Les rats DIO présentent un poids corporel et une adiposité élevés. L'activité physique (aérobie), chez les rats TDIO, améliore ces paramètres. Les rats TDIO montrent des taux réduits de triglycéride et de LDL-cholestérol et des taux élevés de HDL-cholestérol. Les rats DIO présentent une accumulation hépatique élevée de graisses, ce qui est corrigé par l'activité physique. Les mitochondries hépatiques provenant de rats DIO présentent une capacité de β-oxydation plus élevée et une augmentation de la capacité à oxyder le succinate (avec de faibles effets de l'activité physique). Nos résultats démontrent que chez les rats DIO, le développement d'une stéatose précède l'établissement de l'insulino-résistance qui, à son tour, est considérée comme précurseur du développement d'une stéatose hépatique. Cela suggère que certains évènements intrahépatiques pourraient survenir très tôt dans des conditions de nutrition pauvre et probablement contribuer au développement d'une stéatose hépatique non alcoolique (NAFLD). Nos résultats suggèrent que le fait de débuter l'activité physique juste après le sevrage améliore les effets négatifs du régime cafétéria sur la composition corporelle, le profil lipidique et la stéatose.

1. Introduction

Hepatic steatosis is one of the comorbidities frequently associated with obesity and has been considered a novel component of metabolic syndrome, a cluster of several metabolic disorders including obesity, insulin resistance, type II diabetes and hypertension [1,2]. Fatty liver or non-alcoholic fatty liver disease (NAFLD), in turn, has been pointed out as the most frequent cause of chronic liver disease in Western countries [3,4].

In most cases, NAFLD is a benign condition characterized by simple and largely reversible steatosis. However, the steatotic liver becomes vulnerable to secondary insults and it appears to contribute to the occasional progression of NAFLD to more severe and end-stage liver diseases [5,6].

Day and James [7] have proposed the ''two-hit hypothesis'' to explain the development of hepatic steatosis and its progression to inflammation (NASH), fibrosis, and cirrhosis. This hypothesis states that factors such as insulin resistance and impaired hepatic fatty acid oxidation contribute to NAFLD development, and once steatosis is present, both inflammation and oxidative stress are thought to activate stellate cells and increase collagen deposition as well as fibrogenesis.

In fact, accumulating evidences suggests a major role of mitochondria dysfunction in fatty liver, independent of the etiology of the disease [8]. Mitochondrial dysfunction not only impairs fat homeostasis in the liver but also leads to an overproduction of reactive oxygen species (ROS) [9] and cell death through the mitochondrial permeability transition pore (PTP) opening [10].

Liver mitochondrial dysfunction has been described in patients [11] and animal models with hepatic steatosis [12—15], and more frequently in patients with NASH [16]. In all these cases, a decreased capacity of mitochondrial β-oxidation has been considered the cause of fat accumulation — in the form of small droplets of triglycerides — in the cytosol of hepatocytes, characteristic of microvesicular steatosis, which is considered the most aggressive form of NAFLD [17].

The involvement of mitochondrial dysfunction in the pathogenesis of NAFLD becomes more evident from the observation that several drugs and pharmacological agents that, in rodents, suppress β-oxidation directly — by inhibiting mitochondrial enzymes involved in long-chain fatty acids such as CPT-I and long chain fatty acyl-CoA dehydrogenase (LCAD) — or indirectly — by inhibiting the respiratory chain [18,19] — are known to induce hepatic steatosis in humans [20].

Besides steatosis, an increased activity of fatty acid synthase and a reduction in acyl-CoA oxidase and dehydrogenase activities were observed in livers from obese rats treated with cafeteria diet [21].

There is a little information in the literature about the effects of cafeteria diet on rat liver energy metabolism. The assessment of mitochondrial function in this model of steatosis, and the confrontation of the results with those obtained so far in different models of obesity, would allow an evaluation of the role of fat accumulation per se in the mitochondrial function.

In this way, the first purpose of this study was to investigate liver mitochondrial energy metabolism in a model of obesity induced by a hypercaloric cafeteria diet. Histological analyses of livers were conducted, aiming to investigate the existence of a relationship between mitochondrial function and fat liver accumulation. Serum biochemical analysis, including lipid profile, glycaemia, insulinemia and test of glucose tolerance were assessed too.It has long been known that daily exercise prevents most chronic diseases and it is usually recommended for individuals diagnosed with NAFLD and, conversely, a sedentary lifestyle is frequently associated with NAFLD [22—25].Thus, another goal of this research