C. R. Biologies xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Comptes Rendus Biologies

www.sciencedirect.com

Animal biology and pathology/Biologie et pathologie animales

High carbohydrate diet induces nonalcoholic steato-hepatitis (NASH) in a desert gerbil

Induction d'une stéatose hépatique non alcoolique par une alimentation hyperglucidique chez une gerbille désertique

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ARTICLE INFO

Article history:
Received 11 July 2016
Accepted after revision 7 September 2016
Available online xxx

Keywords:
Gerbillus gerbillus
Insulin resistance
Lipogenesis
E.R. stress
Oxidative stress

ABSTRACT

A high intake of sugars has been linked to diet-induced health problems. The aim of this study was to assess whether the long-term consumption of a high-carbohydrate diet (HCD) would cause the hepatic histopathological and metabolic abnormalities that characterize nonalcoholic steatohepatitis (NASH) in a desert gerbil, *Gerbillus gerbillus*. Compared to natural diet, HCD leads to several metabolic disorders including adiposity, dyslipidemia, insulin resistance, ectopic fat deposition in the liver, which were associated with higher levels of transcripts of genes involved with fat synthesis, endoplasmic reticulum (ER) stress, and fibrosis. In the same way, the experimented animals showed enhanced oxidative stress. Taken together, these results demonstrate that HCD consumption in gerbils induces metabolic disorders and damaged liver, which are key contributors to NASH development. These results suggest that this rodent represents a valuable natural model for human diet-induced metabolic disorders and nonalcoholic fatty liver disease (NAFLD).

Mots clés :
Gerbillus gerbillus
Insulino-résistance
Lipogenèse
Stress R.E.
Stress oxydatif

RÉSUMÉ

Les effets d'un régime riche en hydrates de carbone (RHC) sur l'induction de dysfonctionnements métaboliques et d'altérations histopathologiques au niveau du foie caractérisant la stéatose hépatique non alcoolique (NASH) ont été étudiés chez la gerbille *Gerbillus gerbillus*. Comparativement au régime naturel, l'alimentation hyperglucidique induit des perturbations métaboliques marquées par une adiposité, une dyslipidémie, une insulinorésistance et un dépôt ectopique de graisses dans le foie, associé à l'augmentation des ARNm de gènes impliqués dans la synthèse des lipides, le stress du réticulum

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http://dx.doi.org/10.1016/j.crvi.2016.09.002
1631-0691/

endoplasmique et la fibrose. Parallèlement, les animaux expérimentaux développent un état de stress oxydatif. Le RHC induit chez *G. gerbillus* des troubles métaboliques et des lésions hépatiques caractéristiques de la NASH. Nos résultats suggèrent que ce rongeur représente un modèle naturel de choix pour l'étude des dysfonctionnements métaboliques et hépatiques induits par une consommation excessive de glucides chez l'humain.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the main cause of hepatic dysfunction in developed countries and is closely related to components of metabolic syndrome such as obesity, dyslipidemia and type-2 diabetes [1]. Excessive accumulation of triglyceride (TG) in hepatocytes is the hallmark of NAFLD. The spectrum of NAFLD ranges from hepatic steatosis or fatty liver to nonalcoholic steatohepatitis (NASH), liver fibrosis, liver cirrhosis, and eventually hepatocellular carcinoma (HCC) [2]. The precise mechanisms of NAFLD remain poorly understood. The "multiple-hit hypothesis" is currently the most recognized theory to explain disease development and progression, the dysregulation in lipid metabolism being involved in the first hit [3]. It was estimated that 30 % of the TG content in NAFLD livers came from *de novo* lipogenesis, underlying the importance of this pathway in the etiology of NAFLD [4,5]. De novo lipogenesis (DNL) can be triggered by multiple mechanisms, including increased expression of lipogenic enzymes by several specific transcription factors; this is particularly true for members of the SREBP family. One of them, SREBP-1c, controls hepatic DNL primarily by regulation of expression of genes involved in DNL, lipid homeostasis and glucose metabolism [5,6]. Accordingly, hepatic expression of SREBP-1c and its target genes are increased in human fatty liver, compared to healthy individuals [7,8], although DNL is an important determinant of steatosis [9]. The second of the two hits could be due to (1) oxidative stress, (2) proinflammatory cytokines, (3) mitochondrial dysfunction, or/and (4) endoplasmic reticulum stress. Recently, accumulating data have implicated the disruption of endoplasmic reticulum (ER) homeostasis, or ER stress, in both the development of steatosis and progression to NASH [10,11]. ER stress may lead to the activation of various intracellular stress pathways that can initiate or exacerbate insulin resistance (IR) and inflammation and, in some cases, culminate in hepatocyte cell death and liver damage, all of which are important in the pathogenesis of NAFLD. In spite of growing knowledge, several aspects of NAFLD pathogenesis are still unknown.

Considering the difficulty in developing human studies to evaluate the influence of nutrition in the development of NAFLD and associated metabolic abnormalities, animal models constitute a reliable alternative way. Different animal models of NAFLD/NASH have been developed, but few of them replicate the entire human phenotype [12,13]. These models may be classified into three basic categories: those caused by either spontaneous or induced genetic mutation; those produced by either dietary or pharmacological manipulation; and those involving genetic mutation and dietary or chemical challenges. The dietary manipulations used in these last two types of models usually do not resemble the human dietary pattern.

The aim of this study was to determine the long-term impact of high-carbohydrate diet on liver morphology and function in a desert rodent (*Gerbillus gerbillus*). We therefore evaluated the markers involved in metabolic functions, i.e. lipogenesis, fibrosis, ER stress, histopathological changes, and oxidative stress. In the present study, we developed a model of obesity and obesity-related NAFLD in a desert rodent (*G. gerbillus*) using a simple carbohydrate-rich diet.

2. Materials and methods

2.1. Animals and diets

G. gerbillus individuals were collected from the semi-desert Algerian region of Beni-Abbes (30°7' latitude north and 2°10' longitude west). The authorization to capture the animals in desert region was given by the Ministry of Higher Education (Algeria). *G. gerbillus* specimens were maintained under controlled temperature (22 ± 1 °C), humidity (50%) with a fixed 12-h light/dark cycle. After two weeks of acclimatation, the adult gerbils of both sexes were randomly divided into two groups. The control group (n = 6) received a natural diet composed of halophile fresh plants, seeds, dry plants... whereas the experimental group (n = 6) received an HC diet (25 % of barley and 75 % of dried dates) corresponding to a daily caloric intake of 22.5 calories/animal. Details of the composition of the high-carbohydrate diet (HCD) are presented in Table 1. After six months of diet

Table 1
Diet compositions according to Nicole Tonelli and François Gallouin, Fruit and seeds comestibles worldwide, 7th edition. MedPharm Scientific Publishers/Taylor & Francis, 2008.

Nutritional composition	Barley (g/100 g)	Dried dates (g/100 g)
Carbohydrates	**63.30**	**65**
Starch	61.59	–
Simple sugars	1.71	
Glucose	–	25
Fructose	–	25
Saccharose	–	14
Sorbitol	–	1
Protein	11.2	2
Lipids	2.1	0.5
Water	12.2	20
Fibers	9.8	9
Vitamins	0.015	0.012
Minerals & Trace Elements	0.956	0.862
Calories	314 kcal	275 kcal

Please cite this article in press as: N. Semiane, et al., High carbohydrate diet induces nonalcoholic steato-hepatitis (NASH) in a desert gerbil, C. R. Biologies (2016), http://dx.doi.org/10.1016/j.crvi.2016.09.002