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Research paper

Effects of high fat diets on rodent liver bioenergetics and oxidative imbalance

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ABSTRACT

Human metabolic diseases can be mimicked in rodents by using dietary interventions such as high fat diets (HFD). Nonalcoholic fatty liver disease (NAFLD) develops as a result of HFD and the disease may progress in a manner involving increased production of oxidants. The main intracellular source of these oxidants are mitochondria, which are also responsible for lipid metabolism and thus widely recognized as important players in the pathology and progression of steatosis. Here, we review publications that study redox and bioenergetic effects of HFD in the liver. We find that dietary composition and protocol implementations vary widely, as do the results of these dietary interventions. Overall, all HFD promote steatosis, changes in β-oxidation, generation and consequences of oxidants, while effects on body weight, insulin signaling and other bioenergetic parameters are more variable with the experimental models adopted. Our review provides a broad analysis of the bioenergetic and redox changes promoted by HFD as well as suggestions for changes and specifications in methodologies that may help explain apparent disparities in the current literature.

1. Introduction

Human metabolic diseases such as obesity, nonalcoholic steatohepatitis (NASH), and the metabolic syndrome can be mimicked in rodents by using genetic and dietary interventions. Both strategies lead to body weight gain, hyperglycemia, hyperinsulinemia, hepatic steatosis and cardiac impairment [11,32,55]. Dietary models are considered more similar to human metabolic diseases, but there is no standard composition and duration for these diets currently: High fat diets (HFD) range from 30% to 60% energy content in fat, include saturated (SFA), monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) and last from a few days (short term) to over one week (long term) [11,36]. As a result, very variable phenotypes are found in studies in the area, and data are often difficult to compare [11]. For example, the consumption of different types of lipids has a variable effect on the energy expenditure of mammals. Diets rich in SFAs lead to decreased basal metabolic rates, higher body weights and fat gain when compared to diets containing predominantly unsaturated fatty acids [41,54,68]. Furthermore, insulin resistance, an important step in the development of the metabolic syndrome, can be influenced by the lipid content of the diet, occurs more frequently in SFA and MUFA-rich diets and may be minimized by the consumption of PUFAs [10,30,44].

The nutrient overload generated by HFD in experimental animals resembles conditions of overnutrition and physical inactivity that are major risk factors for the development of metabolic syndrome in humans [32,37]. These conditions, when combined, are able to exceed the adipose tissue's ability to handle excessive energy, resulting in an increased efflux of non-esterified fatty acids (NEFAs) and release of proinflammatory cytokines and adipokines that may result in ectopic fat deposition in the liver, muscle and heart [18,74].

In the liver, fat accumulation can be toxic [64,65]. Nonalcoholic fatty liver disease (NAFLD) comprises several liver anomalies related to the accumulation of fat in hepatocytes, including simple steatosis, a benign condition that may progress to serious liver cirrhosis [12,6,65,69]. Currently, the accepted pathophysiological model for NAFLD is the "two hits" model. First, there is accumulation of triacylglycerides (TAG) and free fatty acids (FFA) in the liver as a result of changes in the influx, synthesis, oxidation and transport of fatty acids. The second hit, triggered by the first hit, includes oxidative imbalance, decreased hepatic ATP production, insulin resistance and induction of proinflammatory cytokines as a

Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; CPT1a, carnitine palmitoyltransferase 1; DIO, diet induced obesity; ER, endoplasmic reticulum; ETC, electron transport chain; ETF-DH, electron transfer flavoprotein dehydrogenase; FAO, Food and Agriculture Organization of the United Nations; FFA, free fatty acid; HFD, high fat diet; MUFA, monounsaturated fatty acid; NAFLD, nonalcoholic fatty liver diseases; NASH, nonalcoholic steatohepatitis; NEFA, non-esterified fatty acid; PUFA, polyunsaturated fatty acid; RCR, respiratory control ratio; SFA, saturated fatty acid; TAG, triacylglycerides; UFA, unsaturated fatty acid; VLCAD, very long chain acyl CoA dehydrogenase

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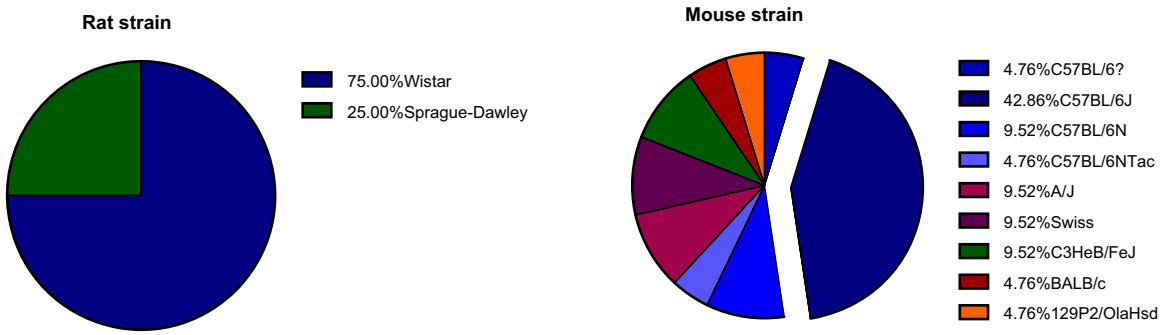

Fig. 1. : Rat and mouse strain distribution in HFD studies.

result of mitochondrial dysfunction, lipid peroxidation and activation of inflammatory pathways as NF-kB and JNK [61,69].

The progression from simple steatosis to NASH involves increased production of reactive oxygen and nitrogen species, lipotoxicity and pro-inflammatory cytokines [7]. The main cellular source of these oxidants is the mitochondrion [37,61], an organelle also responsible for the lipid metabolism, which, consequently, plays an important role in the pathology and progression of steatosis [29,61,6,66]. However, the parameters that characterize what is described as "mitochondrial dysfunction", including changes in oxygen consumption, respiratory complex activity, oxidation of fatty acids and mitochondrial DNA content, differ widely in the literature. In addition to differences between genetic rodent strains of and human polymorphisms, part of the differences observed are probably due to the type and duration of the diet [7].

Given the growing obesity epidemic [53] and the importance of overnutrition in the development of diseases such as the metabolic syndrome and NAFLD [18,37,69], we sought to evaluate and to summarize changes in liver mitochondria related to the consumption of HFD. We collected and discuss papers published over the last 15 years that discussed metabolic changes in the livers of rodents under HFD, focusing on dietary differences and mitochondrial function.

2. Rodents

Although there are some known metabolic differences between rodents and humans, most laboratory metabolic disease studies are conducted in rats or mice because of their inexpensive maintenance, small body size, relatively short lifespan, sequenced genome, and superior physiological characterization compared to other species such as pigs or dogs [2,71]. Studies selected in this review were conducted in rodents, comprising mainly male animals and predominantly C57BL/6 mice (Table 1 and Fig. 1). Reuter [59] defined male C57BL/6J mice as the gold standard for a diet-induced obesity (DIO), and we indeed find it to be the strain used in most papers. These animals are known to develop obesity only under HFD, and metabolic parameters such as glucose intolerance and insulin resistance are worsened over the exposure time to these diets, as is seen in humans [43,59]. A point of notice that should be considered when analyzing data in mice is that the C57BL/6J mice from the Jackson Laboratories, but not C57BL/6 from the National Institute of Health, Taconic Labs or Charles River, carry a spontaneous mutation in the nicotinamide nucleotide transhydrogenase gene that has been implicated in several redox alterations that can affect mitochondrial function [23,62]. C57BL/6N mice do not harbor this mutation.

Table 1
Rodent studies using HFD: sex profiles.

	Mice ($n=31$)	Rats ($n=15$)
Male	24	14
Female	6	0
Both	1	1

Mice and rats generally are started on the HFD at similar ages, and were kept on the diet during widely variable times (Fig. 2). Most of the papers analyzed used paired age groups. Ciapaite et al., 2011, described increased body weights and fasting plasmatic glucose and insulin levels as well as decreased oxidative phosphorylation capacity in 39-week-old animals fed with standard chow diet (9.2% kcal from fat, vegetable oils) in comparison to 16.5-week-old Wistar rats. In addition, Fontana et al. [25], observed that C57BL/6 aged animals (44 and 88 weeks old, fed during 16 weeks with a HFD) did not show increased steatosis compared to their younger counterparts, but exhibited increased inflammation and hepatocellular injury that could contribute to chronic liver disease development and progression. Thus, HFD groups should be paired by diet and also by age to avoid misinterpretation of data.

3. Diets and metabolic profiles

One important critique in HFD treatment is the difficulty to compare studies because of their variability. There are some updated reviews that compare metabolic findings between papers in order to identify the causes of variation and why there is an inability to unify the findings [11,32,43,7]. In this review, we focused only on high energy diets containing fat as the main caloric source. The papers analyzed present a myriad of experimental designs of HFD interventions and significant variation in measured parameters. Diet composition description from controls and high fat groups is often overlooked by the authors and not fully provided in the papers. Due to the lack of information in some papers, a few assumptions were made to facilitate comparisons:

1) Most authors refer to fat content as percentage of energy from fat, since *ad libitum* feeding will be determined by energy requirements [59,60]. However, if the description was made by fat weight and the metabolized energy per weight of food was available, energy from fat was calculated by assuming (as defined by FAO) that 1 g of fat = 9 kcal = 37 kJ (FAO, 2013).
2) Some authors describe the fat content of their diet, including individual fatty acid type. However, most only describe the main source of fat, i.e. lard, vegetable oil, or fish. In addition to the seasonality and origin of the fat, the proportionality trend of fat classes could be defined using the Fat and Oils Handbook [8].

In Table 2, we summarize the percentage of energy from fat of collected studies and in Fig. 3, the main source described by the