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Dietary Type and Amount of Fat Modulate Lipid Metabolism Gene Expression in Liver and in Adipose Tissue in High-fat Diet-fed Rats

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Background and Aims. Dietary fat plays a central role in the development of obesity. However, the metabolic consequences of dietary fat can vary depending on their fatty acid composition. Therefore, the aim of the present work was to study the effect of the type and amount of dietary fat on the expression of genes controlling lipogenesis and fatty acid oxidation in the liver or adipose tissue of rats.

Methods. The expression of hepatic or adipose tissue lipid metabolic genes from Sprague Dawley or Zucker$^{fa/fa}$ rats, respectively, was measured after chronic consumption of diets containing different types/amounts of dietary fats or after rats were adapted for 2 months to a high-fat Western diet and then fed different types and amounts of fats.

Results. Each fat or oil in the diet regulated differentially the expression of transcription factors involved in lipogenesis and fatty acid oxidation as well as some of its target genes in liver. The expression of these genes after a chronic consumption of a high-fat Western diet was reestablished in the presence of less dietary fat and was dependent on the type of fat. In obese Zucker$^{fa/fa}$ rats, consumption of a high-fat diet repressed the expression of lipogenic, fatty acid oxidation and thermogenic genes in adipose tissue.

Conclusions. Type of fat influences the expression of genes that are involved in lipid metabolism in liver and adipose tissue, but this response is repressed when the amount of dietary fat is excessive, diminishing the differences between each type of fat.

Key Words: Adipose tissue, Fatty acids, Fatty acid oxidation, Gene expression, Lipogenesis, Liver disease.

Introduction

Obesity is defined as an excess of adipose tissue in the body, and it is accompanied by metabolic abnormalities including hypertension, hyperlipidemia, and insulin resistance. The appearance of these abnormalities is gradual, and they contribute to degenerative diseases such as cardiovascular disease, nonalcoholic fatty liver disease and type 2 diabetes. These diseases affect many people in most populations of the world including Mexico, presenting serious problems for the healthcare system (1).

The liver and visceral adipose tissue play an important role in the initiation and development of such metabolic disorders. These are the main organs that regulate interorgan lipid metabolism; thus, some of the abnormalities that are characteristic of metabolic syndrome are partially caused by the overaccumulation of lipids in both tissues (2). This overaccumulation leads to a systemic inflammatory state because of the increased recruitment of immune response cells, which in turn increases the release of proinflammatory cytokines (3).

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Overaccumulation of lipids in these organs is in part due to a chronic excess of energy consumption in the form of dietary carbohydrates and fat (4). Consequently, the functions of several transcription factors in the liver and adipose tissue are altered, resulting in the up- or down-regulation of hormones, receptors and enzymes associated with lipid synthesis and oxidation, thermogenesis and cell differentiation, among other processes. Gene expression regulation by dietary fat depends on the interactions between specific fatty acids and transcription factors. Thus, the chain length, degree of unsaturation, and position and configuration of the double bonds of fatty acids differentially activate several transcription factors. This differential activation produces diverse metabolic outcomes (4) as has been demonstrated in clinical trials dating back to the early 1960s (5) as well as in recent studies (6−8).

Several transcription factors are involved in the control of lipid metabolism in the liver. Nonetheless, two transcription factors, sterol regulatory element binding protein-1 (SREBP1-c) and peroxisome proliferator-activated receptor-α (PPAR-α), play key roles in controlling the synthesis and oxidation of fatty acids, respectively (9). These transcription factors upregulate the expression of enzymes that are involved in lipogenesis such as acetyl coenzyme A carboxylase (ACC), fatty acid synthase (FAS) and stearoyl CoA desaturase (SCD-1) (10), as well as enzymes involved in β-oxidation such as acyl coenzyme A oxidase (ACO), medium-chain acyl-CoA dehydrogenase (MCAD) and carnitine palmitoyl transferase 1 (CPT-1) (11,12).

The transcriptional regulation of lipid metabolism in adipose tissue also involves SREBP-1C and PPAR-α (13,14). The transcription factor PPAR-γ is also required to maintain the differentiated state of adipocytes (15). The function of these transcription factors is essential to maintain a functional adipose tissue capable of maintaining all the indispensable tasks of an adipocyte (16,17).

In animal models, polyunsaturated fatty acids (PUFAs) can specifically downregulate the expression of lipogenic genes, whereas saturated fatty acids (SFAs) can stimulate their expression (9,18,19). PUFAs are strong ligands of PPAR-α and stimulate the expression of genes involved in fatty acid oxidation and thermogenesis (9,18−20). In addition, the expression of PGC-1α (PPAR-γ coactivator-1α), a transcriptional coactivator of PPAR-α necessary for the overexpression of enzymes that control fatty acid oxidation, is downregulated in response to a diet high in SFA (21).

Previous studies have investigated the regulation of gene expression in adipose tissue by PUFAs (9). Dietary SFA, trans-fatty acids and high-fat diets downregulate glucose transporter 4 (GLUT4) mRNA in white adipose tissue, an effect that is attenuated by a high-fat diet rich in ω-3 PUFAs (22,23). However, the effect of PUFAs is different in subcutaneous fat and in visceral adipose tissue (24).

Despite the evidence for the clinical effects of dietary fats, epidemiological studies are still controversial when considering the association between fat composition and changes in weight and/or body fat composition, rate oxidation or energy expenditure (4). Moreover, the expression of lipid metabolism-related genes in the liver and in adipose tissue related to weight and metabolic changes also remains controversial (25). Thus, in order to answer these controversial issues, the aims of this study were 1) to characterize the expression of genes of lipid synthesis and oxidation regulated by the transcription factors SREBP-1 and PPAR-α in liver after the chronic consumption of different types of fats composed of fatty acids with distinct chain length and degree of unsaturation such as chia oil, soybean oil, corn oil, safflower oil, lard, shortening, butter and coconut oil (Study 1); 2) to determine if after a chronic consumption of a high-fat Western diet containing also cholesterol, the altered expression of these genes in liver is reestablished in the presence of distinct amounts of fat from different sources (chia oil, soybean oil and butter) (Study 2); 3) finally, besides liver, adipose tissue also plays an active role in maintaining lipid homeostasis, so in order to identify the alterations in the expression of genes involved in lipid synthesis and oxidation, thermogenesis and adipogenesis, their expression was measured in adipose tissue of an obese rat model when consuming a high-fat diet, rich in polyunsaturated or saturated fatty acids (Study 3).

Materials and Methods

Study 1

In order to study the expression of genes involved in hepatic lipid synthesis and oxidation after consumption of a high-fat diet for an extended period with different fat sources, each containing a specific pattern of fatty acids, 40 male Sprague Dawley rats weighing 120 g were housed in individual metallic wire cages with free access to food and water for 2 months. Rats were divided into eight experimental groups of five rats each that were fed for 2 months with a diet containing 20% casein and 10% of a specific fat source as described in detail in Table 1: 1) chia oil, 2) soybean oil, 3) corn oil, 4) safflower oil, 5) lard, 6) shortening, 7) butter and 8) coconut oil (see Table 1). This amount of fat is twice the amount required to maintain the rats according to AIN-93 and to the U.S. National Research Council (26,27). Because AIN-93 recommends soybean oil as the standard source of fat in a rodent diet, gene expression was analyzed relative to the soybean oil group.

Body weight gain and food intake were recorded every day. At the end of the study, rats were fasted overnight and livers were immediately removed and frozen at −70°C for