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Role of thyroid hormone homeostasis in obesity-prone and obesity-resistant mice fed a high-fat diet

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ABSTRACT

Background. The exact mechanism for different propensities to obesity when consuming a high-fat diet (HFD) is largely unknown. Thyroid hormone (TH) is an important modulator of energy homeostasis and body weight.

Objective. The present study aimed to find the potential mechanisms of TH in the development of obesity-prone (OP) and obesity-resistant (OR) mice after short-term and long-term HFD feeding.

Methods. C57Bl/6 male mice were randomly divided into two groups: a low-fat diet (LFD) group and an HFD group. In the 7th week, HFD-fed mice were classified as OP or OR according to upper and lower tertiles of body weight. Half of the mice were sacrificed at this time point and the remaining mice were kept on feeding and sacrificed in the 27th week. Indirect calorimetry was performed. At harvest, serum was used for ELISA assays and oxidative stress biomarkers determination. Tissues were dissected for deiodinases activity and relative mRNA expression determination, as well as antioxidant capacity evaluation.

Results. In the 7th week, OP mice showed a significant body weight gain, decreased energy expenditure (EE), normal circulating TH levels, and activated HPT axis, whereas OR mice had normal body weight and maintained T_3 levels only through enhancing hepatic D1 activity. In the 27th week, OR mice gained more body weight than LFD mice accompanied by an activation of HPT axis and decreased hepatic deiodination. Genes involved in TH production were down-regulated in OP mice and up-regulated in OR mice. Changes in deiodinases activity and thyroid function were related with redox status in specific tissues. Furthermore, OP mice had more serious hepatic steatosis than OR mice, with up-regulation of T_3 target genes (*e.g. Srebp1c, Acc1, Fasn*) involved in lipid synthesis and down-regulation of *Pgc1α*, *Cyp7a1* and *Cpt1α*.

Conclusions. HPT axis function and deiodinases activity might be involved in different propensities to obesity and the ability of OR mice to resist obesity was limited.

Abbreviations: D1, type 1 deiodinase; D2, type 2 deiodinase; DIO, diet-induced obesity; EE, energy expenditure; FBG, fasting blood glucose; FFA, free fatty acids; Gpx, glutathione peroxidase; HFD, high-fat diet; HPT axis, hypothalamus–pituitary–thyroid axis; LFD, low-fat diet; OP, obesity-prone; OR, obesity-resistant; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; TC, total cholesterol; TG, triglycerides; TH, thyroid hormone; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone.

Conflict of interest: The authors have no conflict of interest.

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1. Introduction

Obesity, a condition of energy imbalance between energy intake and expenditure, is becoming a common health problem in the affluent countries, and represents one of the most prevalent risk factors for the development of common chronic metabolic diseases, such as cardiovascular disease and diabetes [1]. Accumulating evidences have shown that weight gain is a "normal" response to the modern environment and that the weight regulatory system is biased toward obesity [2]. Some individuals become obese easily (obesity-prone, OP) and others keep resistant to obesity (obesity-resistant, OR) when exposed to high-fat diets (HFD), and the propensities vary widely among individuals, both across and within species or strains [3–5]. Studies focused on OP and OR animals indicated that OP animals tend to show fat storage or decreased fatty acid oxidation compared to OR control [6]. Although several hypotheses have been proposed, including physiological signaling and responsiveness, genetic differences, metabolic processes [7,8], the exact mechanisms underlying interindividual susceptibility to diet-induced obesity (DIO) are largely unknown. Revealing the peculiar features that prevent OR individuals from developing an excess of body weight despite the HFD, might suggest a new solution for the pharmacological treatment of diet-induced obesity.

Thyroid hormone (TH) is an important modulator of lipid metabolism and metabolic rate, favoring lipolysis and increasing the use of fatty acids as fuels, resulting in reduced fat accumulation and body weight. Therefore, oscillations in circulating and tissue-specific levels of TH are expected to result in profound alterations in metabolic rate. Researchers are becoming interested in investigating whether an increase of body weight might be related to an underlying thyroid disturbance [9–11]. Changes in TH in obesity have been reported [12]. Although there is no consensus regarding the serum profile of TH in obesity, the disruption of the normal hypothalamus–pituitary–thyroid (HPT) axis function is a consensus, which could be caused by: a) dysfunction of the hypothalamic–pituitary axis; b) modifications in thyroid gland function per se and/or; c) alterations in iodothyronine deiodinase activities in central and peripheral tissues. It is also clear that TH levels in the plasma hardly fluctuate in healthy humans and do not represent TH signaling in cells; TH-responsive metabolic processes are turned on and off by TH via deiodination pathways that take place inside the target cells [13]. Therefore, the regulation of steps involved in the control of secretion and deiodination of TH is expected to play dominant roles in defining the energy balance under HFD feeding, which might be the possible mechanisms for the differentiation of OP and OR phenotypes.

It has been demonstrated that thyroid gland requires a certain amount of H_2O_2 for TH synthesis [14], which is commonly considered to be harmful to other organs. Redundant reactive oxygen species (ROS) are detrimental to iodine uptake [15] and may disorder thyroid TH synthesis. Besides, oxidative stress could decrease deiodinases activity (mainly type 1 and type 2 iodothyronine deiodinases, D1 and D2) [16], whereas antioxidant supplementation could partially restore D1 activity [17], leading to the possibility that oxidative stress might play an important role in TH homeostasis. Therefore, we speculated that OR individuals might have a more balanced redox status to better maintain TH homeostasis than OP mice, resulting in increased energy expenditure and/or reduced energy intake to keep a lean phenotype. However, whether OR individuals can always keep resistant to obesity on condition of long-term HFD consumption is uncertain. The present study focused on oxidative stress related HPT axis function and deiodinases to achieve a detailed understanding of molecular mechanism underlying diverse propensities to DIO between OP and OR mice.

2. Materials and methods

2.1. Animals

C57Bl/6 male mice (280, 4-week-old) were obtained from Model Animal Research Center of Nanjing University (Nanjing, Jiangsu, China) and housed individually in a controlled environment (a 12-/12-h light/dark cycle, 08:00 h to 20:00 h, humidity: 60 ± 5%, temperature: 23 ± 2 °C). After acclimatization for one week on standard laboratory chow, all mice were randomly assigned into two groups and fed *ad libitum* either a low-fat diet (LFD, n = 70. 70, 20 and 10% of calories from carbohydrate, protein, and fat, respectively, energy density 3.85 kcal/g) and a saturated high-fat diet (HFD, n = 210, 35, 20, and 45% of calories from carbohydrate, protein and fat, respectively, energy density 4.73 kcal/g). All diets were purchased from Research Diets (New Brunswick, NJ, USA). All mice had free access to the test diets and purified water throughout the experiment. In the 7th week, mice that were fed the HFD were classified by body weight into OP and OR mice, according to the method used previously [18,19]. The mice (n = 70, 34.85 ± 1.04 g) in the upper tertile of body weight were numbered and selected as OP and those in the lower tertile (n = 70, 24.54 ± 1.18 g) were numbered as OR. 35 mice from OP and OR groups that had odd numbers with another 35 mice randomly selected from LFD group were sacrificed to evaluate the effects of short-term HFD feeding on the differentiation between OP and OR groups; the remaining mice that had even numbers were kept on their respective diets for a further 20 weeks and then sacrificed to evaluate the long-term effects of HFD. During the course of the feeding, all mice were weighed weekly, and food intake also recorded. The study was carried out in accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals of the Institutional Animal Care and Use Committee of Jiangnan University.

2.2. Indirect calorimetric analysis

The Comprehensive Laboratory Animal Monitoring System (C.L.A.M.S.; Columbus Instruments, Columbus, OH) was used to evaluate respiratory exchange ratio (RER), energy expenditure (EE = (3.815 + 1.232 × RER) × VO_2), ambulatory activity and food consumption according to the published literature [10]. One week before the end of their respective dietary manipulation, the eight mice with the highest body weight in OP mice