Biochimica et Biophysica Acta 1863 (2017) 1147–1155

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Western-style diet, sex steroids and metabolism☆

Oleg Varlamov *

Division of Diabetes, Obesity, and Metabolism, Oregon National Primate Research Center, Beaverton, OR 97006, United States

ARTICLE INFO

Article history:
Received 14 April 2016
Received in revised form 27 May 2016
Accepted 28 May 2016
Available online 3 June 2016

Keywords:
Western-style diet
High-fat diet
Hypogonadism
PCOS
Sex hormones
Menopause

ABSTRACT

The evolutionary transition from hunting to farming was associated with introduction of carbohydrate-rich diets. Today, the increased consumption of simple sugars and high-fat food brought about by Western-style diet and physical inactivity are leading causes of the growing obesity epidemic in the Western society. The extension of human lifespan far beyond reproductive age increased the burden of metabolic disorders associated with over-nutrition and age-related hypogonadism. Sex steroids are essential regulators of both reproductive function and energy metabolism, whereas their imbalance causes infertility, obesity, glucose intolerance, dyslipidemia, and increased appetite. Clinical and translational studies suggest that dietary restriction and weight control can improve metabolic and reproductive outcomes of sex hormone-related pathologies, including testosterone deficiency in men and natural menopause and hyperandrogenemia in women. Minimizing metabolic and reproductive decline through rationally designed diet and exercise can help extend human reproductive age and promote healthy aging. This article is part of a Special Issue entitled: Oxidative Stress and Mitochondrial Quality in Diabetes/Obesity and Critical Illness Spectrum of Diseases - edited by P. Hemachandra Reddy.

1. Introduction

The transition of *Homo sapiens* from hunting and gathering to a farming society during the Neolithic period resulted in a dietary shift to carbohydrate-rich diets [1]. The development of agriculture, animal domestication and technological progress significantly lowered the cost and availability of food supply, creating a unique situation in the history of human evolution when caloric intake exceeded energy expenditure. Today, reduced physical activity and the increased consumption of calorie-dense food are being recognized as the main risk factors responsible for the growing epidemic of obesity in the modern society [2,3]. As a result of the spreading influence of the Western-style diet (WSD), enriched in simple carbohydrates and saturated fats, the worldwide prevalence of obesity almost doubled between 1980 and 2014 [4]. WSD represents the calorie-dense food, highly heterogeneous in quantities and qualities of fat (saturated vs unsaturated), carbohydrates (high glycemic vs low glycemic), and protein content. Recent evidence suggest that imbalance in the levels of sex steroids is associated with metabolic disorders, such as obesity and insulin resistance. Given that diet plays a pivotal role in the regulation of energy metabolism, it is timely to discuss the contribution of a WSD, as a pathophysiological risk factor, in the progression of sex-hormone-related metabolic pathologies.

2. Sex hormones and energy metabolism

Speaking in evolutionary terms, the drive to eat excessively represents an ancient biological instinct, which plays a crucial role in successful reproduction and survival in calorie-sparse environment. Studies in numerous organisms demonstrate that reduced or abolished reproductive function results in excess body fat and longer lifespan [5,6], representing a potential adaptive mechanism for surviving short starvation periods, when population integrity is achieved via the extension of the lifespan of individuals as a trade-off between limited food supply and reduced reproduction (Fig. 1, "Starvation" and "Limited calorie supply"). This biological principle is evolutionary conserved from single-cell organisms to mammals [7]. As demonstrated in multiple organisms, including worms, flies, mice and monkeys, caloric restriction can extend lifespan [8,9] and reduce reproductive potential (Fig. 1). Both peripheral hormones and central neuropeptides regulating energy balance have been postulated to play a role in suppressing hypothalamic circuits regulating reproductive function during conditions of low energy availability [10,11]. A modest and/or transient increase in body fat can benefit survival by providing energy in calorie-deficient environment (Fig. 1, "Limited calorie supply"). However, chronic calorie surplus and excess body fat is not beneficial but detrimental for survival because of increased mortality from metabolic, cardiovascular diseases, and other obesity-associated

Abbreviations: ADT, androgen deprivation therapy; PCOS, polycystic ovary syndrome; WSD, Western-style diet; WAT, white adipose tissue.

☆ This article is part of a Special Issue entitled: Oxidative Stress and Mitochondrial Quality in Diabetes/Obesity and Critical Illness Spectrum of Diseases - edited by P. Hemachandra Reddy.

* Oregon National Primate Research Center, 505 NW 185th Ave., Beaverton, OR 97006, United States.
E-mail address: varlamov@ohsu.edu.

http://dx.doi.org/10.1016/j.bbadis.2016.05.025
0925-4439/

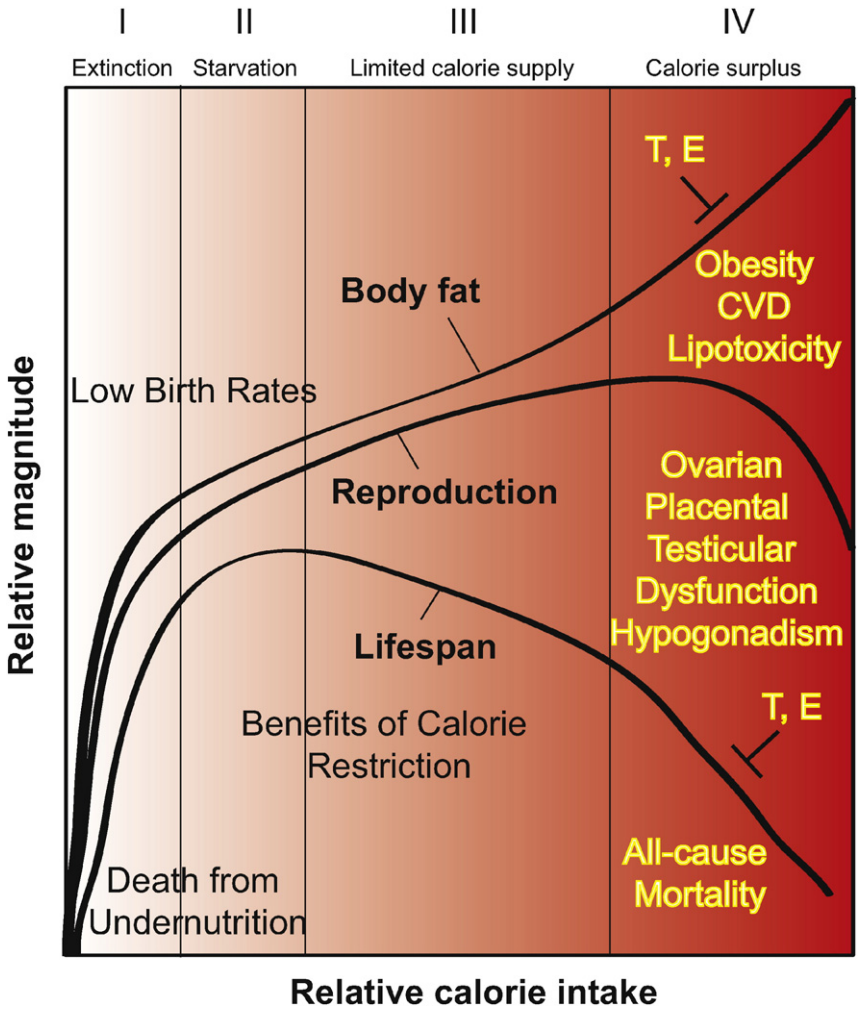

Fig. 1. Regulation of reproduction and lifespan by calorie intake. *X-axis*, relative calorie intake is represented by red gradient, ranging from starvation (left part of the graph) to overnutrition (right part of the graph). *Y-axis*, relative magnitude of each biological process (lifespan, reproductive function and fat storage). ***Sector I,*** chronic calorie deficiency reduces survival, as a result of lower birth rates and higher death rates from undernutrition. Extreme starvation can reduce population size and lead to extinction. ***Sectors II and III,*** during starvation or limited calorie supply, reduced reproduction results in longer lifespan. The latter is brought about by the beneficial effects of caloric restriction on lifespan (mechanisms are unknown) and healthspan (reduced metabolic disease). The suppression of reproductive function during the negative energy balance is mediated by the central hypothalamic mechanism. ***Sector IV***, chronic calorie oversupply results in obesity, which increases metabolic and reproductive dysfunctions and all-cause mortally, resulting in shorter lifespan. Obesity is associated with reduced sex hormone levels, resulting in worsening metabolic dysfunction. Testosterone (T) and estrogens (E) protect males and females from metabolic disease through central and peripheral mechanisms. This graph is designed to provide *only* a schematic illustration of biological relationships.

conditions (Fig. 1, "Calorie surplus"). Gonadal steroids, also known as sex hormones, play a dual role regulating both reproductive function and energy metabolism in males and females.

2.1. Estrogens

Normal estrogen production is generally associated with reproductive and metabolic health in females, protecting against metabolic disease and obesity (Fig. 1, "E, Caloric surplus and Table 1)". In mice, estrogen depletion via gonadectomy or aromatase deletion results in excess body fat, insulin resistance and mitochondrial dysfunction, whereas estrogen replacement can protect estrogen-deficient mice from metabolic disease [12–16]. Increased fat storage observed in gonadectomized female mice is consistent with studies in invertebrates, including *Caenorhabditis elegans* and *Drosophila melanogaster* [5,6]. Many anorexic effects of estrogens are mediated by the hypothalamic estrogen receptor-α (ERα), which regulates energy expenditure, food intake, and glucose homeostasis (Fig. 2, Table 1 and [17–19]), while diminished ERα activity induces obesity and insulin resistance in mice [20–22]. In peripheral tissues, estrogens promote lipid mobilization through inhibition of lipogenesis in the liver and stimulating triglyceride breakdown in white adipose tissue (WAT) [23–25]. Furthermore, estrogens can protect β-cell function in ovariectomized females [26] and obese males [27] and reduce streptozotocin-induced β-cell injury in both sexes [28,29]. Hence, estrogens are sex-specific metabolic regulators that defend female organism from the metabolic stress of overnutrition and obesity during the positive energy balance (Fig. 1, "Caloric surplus" and Fig. 2, right). In contrast, during the negative energy balance, female reproductive status is suppressed while caloric restriction become beneficial for survival through the extension of healthspan and/or lifespan (Fig. 1, "Starvation").

2.2. Progesterone

Although the role of progesterone in female metabolism is less defined, this steroid hormone can be viewed as a functional antagonist of estrogens (Fig. 2, right). Cyclic changes in estrogens and progesterone levels during menstrual cycle may reflect the periodic adjustment of female metabolism to metabolic burden associated with ovulation and gestation. Glucose utilization is higher during the follicular phase (high estrogen-to-progesterone ratio) and low during the luteal phase (high progesterone-to-estrogen ratio) [30]. Estrogens increase insulin