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Review

Sexual differences in the control of energy homeostasis

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ABSTRACT

The prevalence of obesity has reached epidemic proportion with enormous costs in both human lives and healthcare dollars spent. Obesity-related metabolic disorders are much lower in premenopausal women than men; however, there is a dramatic increase following menopause in women. The health risks associated with obesity vary depending on the location of adipose tissue. Adipose tissue distributed in the abdominal visceral carry a much greater risk for metabolic disorders than does adipose tissue distributed subcutaneously. There are distinct sex-dependent differences in the regional fat distribution, women carry more fat subcutaneously whereas men carry more fat viscerally. Males and females differ with respect to their regulation of energy homeostasis. Peripheral adiposity hormones such as leptin and insulin as well as sex hormones directly influence energy balance. Sexual dimorphisms in energy balance, body fat distribution, and the role sex hormones have in mediating these differences are the focus of this review.

1. Introduction

1.1. Incidence of obesity and its related metabolic disorders

1.1.1. Male vs. female

The increasing prevalence of obesity throughout the world [51,122,127] is associated with an escalating incidence of obesity-related disorders and health costs [5]. Obesity is a leading cause for the development of adverse metabolic effects, including non-insulin dependent diabetes mellitus, dyslipidemia, and cardiovascular disease [34,45]. It has been estimated that 47 million individuals in the United States have obesity-related metabolic diseases [53]. There are important sex differences in the prevalence of these metabolic diseases. Women under the age of 50 have much less obesity-related metabolic disorders; however, the prevalence of these metabolic disorders increases dramatically in women after menopause [52]. Children who have metabolic diseases have a higher risk of developing adverse events later in life [55,116]. In today's society there is an increase in the prevalence of obesity and its related metabolic diseases in adolescents and it is significantly higher among males than females aged 12–18 years [54,70,154]. Data suggest that ovarian hormones may be protective against the metabolic syndrome because prior to menopause, the prevalence of the metabolic disorders is higher among males than females; however, after menopause, women are more likely to suffer from metabolic disorders.

1.1.2. Visceral fat vs. subcutaneous fat

The increased health risks due to obesity vary depending on the location/accrual of adipose tissue [15–17,19,123]. Specifically, adipose tissue distributed in the abdominal or visceral region carries a much greater risk for metabolic disorders, than does adipose tissue distributed subcutaneously [19–21]. Differences in distribution of adipose tissue and the relative risk for diseases suggest that not all adipose tissue is created equally. Rather, different adipose depots have different properties that can have important consequences on health outcomes.

There are distinct sex-dependent differences in the regional fat distribution. If age and body mass index (BMI) are matched, women have lower waist-to-hip ratio, indicating a greater amount of subcutaneous adipose tissue than men do [95,117]. Excess adiposity in the central visceral region of the body ('android' or male-pattern obesity [167]) is correlated with increased risk and mortality from disorders including diabetes, hyperlipidemia, hypertension, and atherosclerosis [11,56,73]. In contrast, excess adiposity in the gluteal/femoral subcutaneous region ('gynoid' or female-pattern) is poorly correlated with risk for these metabolic disorders [18,39,40,88,123]. Hence, there are sex-based differences with regard to obesity-associated health risks with obese men being more likely to develop secondary metabolic complications and cardiovascular diseases than obese women [36,83,87,92,169]. Therefore, the distribution of fat is more directly associated with the metabolic syndrome than total body fat.

There are two important implications that follow from these observations. The first is that males and females may differ in their susceptibility to the metabolic syndrome based on where they de-

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posit adipose tissue. The second is that whereas we know the health consequences associated with visceral fat deposition, very little is known about how excess nutrients are partitioned/stored into the different adipose tissue depots. The goal of this review is to explore what we know about these sex differences in energy balance which are associated with adipose tissue accrual and deposition, as well as the role that sex hormones play in these differences.

2. Sex differences in body fat distribution

2.1. Sex steroids regulate fat distributions

As previously mentioned, on average, women carry more fat subcutaneously [42,66,80,89,90]; whereas men carry more fat viscerally [167]. Gonadal/sex steroids have been proposed as regulators of fat distribution [47,48]. Men have lower estrogen, and on average, men also have less total fat and a more central or intra-abdominal distribution; whereas premenopausal women have more total fat and a more gluteal/femoral subcutaneous fat distribution (Fig. 1). Intra-abdominal fat varies inversely with estrogen levels [12,13,15,25,49]. After menopause and the decline of estrogen, women develop increased intra-abdominal adiposity, but those who receive estrogen replacement therapy do not [59,63,64], suggesting a specific role of estrogen in limiting intra-abdominal fat mass [10,31]. Androgens favor abdominal fat deposition. Most women with polycystic ovary syndrome (PCOS), a hyperandrogenic disorder, have increased abdominal fat [37]. Exaggerated androgen synthesis and secretion by the ovaries and the adrenal glands are associated with insulin resistance and impaired glucose tolerance [37]. Consequently women with PCOS have increased risk for the metabolic syndrome. Given these differences in body fat distribution and co-morbidities, it is likely that the mechanisms that regulate body fat distribution differ in males and females.

2.2. Differences in subcutaneous vs. visceral fat

2.2.1. Lipid mobilization (lipolysis) vs. lipid accumulation (lipogenesis)

In all mammalian species, energy is primarily stored in the form of lipid in white adipose tissue. The amount of fat stored in adipose tissue is the net difference between the rates of lipogenesis and lipolysis. In situations where metabolic fuels are not sufficient to meet energy needs, a lipolytic cascade is initiated that results in the breakdown of energy stored in the form of triglycerides into free fatty acids and glycerol via hormone-sensitive lipase, the enzyme that turns on lipolysis. Catecholamines trigger lipolysis via membrane-bound α- and β-adrenoceptors [27,85]. Specifically catecholamines stimulate lipolysis via β1-, β2- and β3-adrenoceptors and inhibit lipolysis via α2-adrenoceptors [27,85]. Lipolysis correlates positively with activation of the sympathetic nervous system [4] which may further enhance free fatty acid release into portal circulation [95]. In situations where there is a prolonged positive energy balance, adipocytes take up circulating fatty acids and this leads to increases in both adipocyte size and number, which is manifested more generally as an increased body fat mass [50]. The major pathway of free fatty acid uptake is mediated by lipoprotein lipase, an enzyme that hydrolyses meal-derived triglycerides in chylomicrons and very low density lipoprotein triglyceride at the capillary endothelium. In addition, circulating free fatty acids are directly taken up and stored via a lipoprotein lipase-independent pathway [9,32,142].

There are sex differences in the lipolytic response. Female rats have higher lipolytic capacities and a lower α2/β3-adrenoceptor ratio in intra-abdominal retroperitoneal adipose tissue than male rats [94]. High-fat diet feeding changes α2- and β3-adrenoceptors differentially in males and females, specifically, in males there is an increase in antilipolytic α2-adrenoceptor and reductions in lipolytic β3-adrenoceptor in female rats. In addition, the decrease of α2/β3-adrenoceptor ratio is greater in males than females, which leads to a greater amount of fat accumulation in males fed with a high-fat diet [94]. In humans, lipolytic response of abdominal

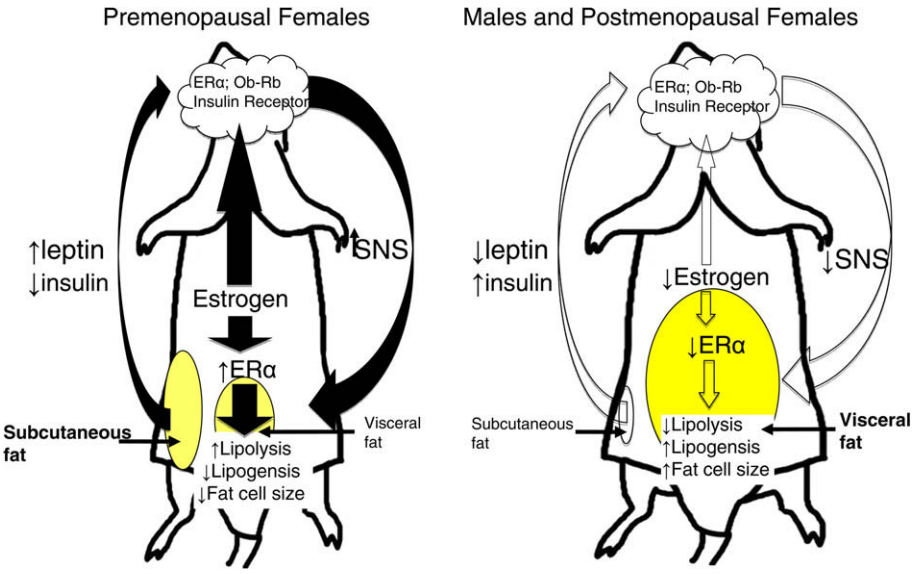

Fig. 1. Potential model depicting how sex hormones and adiposity signals may interact to regulate body fat distribution. We propose that female sex steroid estrogen regulates body fat distribution. Females carry more fat subcutaneously whereas males with lower estrogen carry more fat viscerally. Reductions in estrogen, as occurs in menopause, is associated with an increase in visceral adiposity. Estrogen receptors (ER) are expressed in adipose tissues and hypothalamus. Estrogen regulates energy balance and body fat distribution by either directly interacting with the leptin signaling pathway or through activation of estrogen receptors. Specifically, estrogen may directly act on estrogen receptor alpha (ERα) in visceral adipose tissues to regulate lipid metabolism. Estrogen may influence adiposity by interacting with leptin, and potentially enhancing leptin-induced activation of the sympathetic nervous system which innervates visceral adipose tissue, thereby reducing fat accrual in the visceral depot. Additionally, subcutaneous adipose tissue, which accounts for a higher percentage of adipose tissue in females, secretes leptin, and the secreted leptin may activate CNS leptin receptors, and this may directly influence leptin-induced activation of the sympathetic nervous system.