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Review

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Leptin in normal physiology and leptin resistance

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Abstract Since the discovery of leptin as an adipokine in 1994, much progress has been made in the research about leptin. Circulating leptin binds to leptin receptor, activates STAT3-dependent and STAT3-independent signaling pathways, and plays an effective role in energy homeostasis, neuroendocrine function and metabolism mainly through acting on the central nervous system, especially the hypothalamus. Leptin resistance is considered as a key risk factor for obesity. Various mechanisms have been formulated in order to explain leptin resistance, including impairment in leptin transport, attenuation in leptin signaling, ER stress, inflammation and deficiency in autophagy. Here, we review our current knowledge about leptin action, leptin signaling and leptin resistance, hoping to provide new ideas for the battle against obesity.

Keywords Leptin biology · Leptin function · Leptin signaling · Leptin resistance · Energy homeostasis

1 Introduction

The past decades have witnessed an explosion of the incidence of obesity. Estimates from the World Health Organization (WHO) indicate that worldwide obesity doubled between 1980 and 2008, and as of 2014, at least 600 million adults were obese. Obesity is very closely associated with a myriad of comorbidities, which include hypertension, type 2 diabetes, cardiovascular disease and many types of cancers [1]. Elucidating the mechanisms underlying obesity is urgent and critical in the fight against obesity.

Obesity is characterized by an expanded adipose tissue mass. There are two kinds of adipose tissue: white adipose tissue (WAT) to store energy and brown adipose tissue (BAT) to dissipate energy [2]. BAT has an especially important function in newborns, but gradually disappears or become inactive with age [2]. WAT is not only the largest energy reserve, but also the largest endocrine organ in the body. It has been clearly demonstrated that adipose tissue produces a variety of adipokines and cytokines that regulate important biological processes [3]. Among them, leptin is the first one to be found [4].

The discovery of leptin could be considered the initial milestone for adipokine research. In 1950 and 1966, respectively, two kinds of obese mice derived from homozygous mutations of *ob* and *db* gene were produced in Jackson laboratory [5, 6]. These mice were massively obese, with hyperglycemia, hyperinsulinemia, insulin resistance and peripheral neuropathy [4]. Through parabiosis experiments, scientists postulated the existence of a satiety factor to act on the hypothalamus to regulate food intake and energy consumption [7, 8]. In 1990, successful mapping of the *ob* and *db* gene was reported [9, 10]. Then finally in 1994, Friedman's laboratory cloned *ob* gene through positional cloning [4]. Friedman named this new hormone as "leptin" from the Greek root "lepto", meaning "thin" [11]. A report in 1995 proved that the *db* gene encodes the leptin receptor [12]. Today we know that while ob/ob mice possess a single nonsense mutation in the *ob* gene, leading to a truncated nonfunctional form of leptin

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[4], db/db mice have an insertion mutation in the *db* gene that interferes normal splicing of the leptin receptor [13].

In this review, we will focus on leptin function, leptin signaling and recent advances in understanding the possible mechanisms underlying leptin resistance.

2 Leptin biology

Leptin, located on chromosome 7, is a 167-amino acid polypeptide, and molecular weight is 16 kD [14]. It is mainly synthesized and secreted by WAT. However, the placenta, ovary, skeletal muscle, mammary epithelium, bone marrow and lymphoid tissue could also express leptin [15, 16]. The circulating leptin levels are positively correlated with the amount of body fat [17]. Particularly, subcutaneous fat expresses more leptin compared with visceral fat [18]. Women tend to have higher leptin levels than men probably due to larger subcutaneous fat and the influence of sex hormone [19]. Leptin levels also fluctuate according to energy state, with a marked decrease during starvation and an increase in energy surplus states [20]. Other factors including hormones (insulin, estrogen, glucocorticoids, etc.), metabolites (glucose, fatty acid, etc.) and inflammatory cytokines also influence leptin secreting and expression [21–24] (Fig. 1). Besides, leptin levels display a circadian rhythm, with lowest levels in around noon to midafternoon and highest levels between midnight and early morning [25].

Leptin receptor (LepR) belongs to long-chain helical cytokines superfamily. Via alternative splicing, *Lepr*, or *db* gene, produces six LepR isoforms (LepRa, b, c, d, e and f) [12, 26]. These isoforms possess the same extracellular domain, but differ by their transmembrane and cytoplasmic domains. LepRb is the only form that contains intracellular motifs of approximately 300 amino acid residues. It is ubiquitously expressed in the body and mediates the main effects of leptin on controlling energy homeostasis and body weight [16]. Besides LepRb, the short isoform LepRa also plays essential roles in mediating leptin internalization and signaling [27, 28]. LepRe is soluble and inhibits the transportation of leptin across the blood–brain barrier (BBB) by reducing the endocytosis of leptin [29].

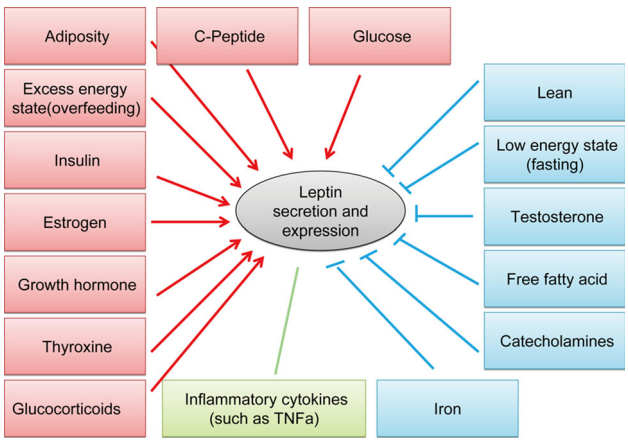

Fig. 1 Factors regulating circulating leptin levels. Notes: The red boxes indicate factors that promote leptin secretion and expression. The blue boxes indicate factors that suppress leptin levels. The green box indicate factor that influences leptin level differently according to the microenvironment

3 Leptin function

Leptin acting on specific populations of neurons in the brain, including hypothalamic, midbrain and brainstem neurons, plays a central role in energy homeostasis and neurofunction [30–32]. Besides, leptin also has multiple roles in metabolism, reproductive system, immune function, etc. [15, 32–35].

3.1 Leptin and the central nervous system

The function of leptin on controlling energy homeostasis and body weight is mainly conducted by the central nervous system. In addition to reducing energy intake via central regulation of appetite and satiety, leptin also promotes energy expenditure and mediates neuroendocrine function and cognition [32].

The leptin receptor LepRb is highly expressed in the brain, particularly in the arcuate (ARC), dorsomedial (DMH), ventromedial (VMH) and ventral premamillary nuclei (PMV) of hypothalamus [36, 37]. Also, these leptin-responsive neurons (designated as the first-order neurons) broadly connect to other neurons in the brain, thus forming a sophisticated neural network [30]. The ARC of the hypothalamus is a critical site of leptin action. Actually, LepRb expression was co-localized with two neuronal populations of ARC: anorexigenic proopiomelanocortin (POMC) neurons and orexigenic agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons [38]. Leptin signaling activation directly stimulates POMC neurons and thus releases α-melanocyte-stimulating hormone (α-MSH) [30]. α-MSH is an anorexigenic neuropeptide that decreases food intake by binding to and activating melanocortin-4 (MC4R) [39]. On the other side, leptin also inhibits orexigenic neuropeptides AgRP and NPY, which antagonize the α-MSH/MC4R signaling and thus reduce appetite [40]. Recent literature suggests leptin inhibits the rewarding effects of running via LepR-STAT3 modulation of dopamine tone, maybe as an adaptive means to reduce the motivation for feeding [41]. The role of leptin in promoting energy expenditure is mediated by activation of the