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Review

Leptin and the hypothalamo-pituitary–adrenal stress axis

Eric W. Roubos *, Maurice Dahmen, Tamás Kozicz, Lu Xu

Department of Cellular Animal Physiology, Faculty of Science, Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, P.O. Box 9010, 6500 GL Nijmegen, The Netherlands

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ABSTRACT

Leptin is a 16-kDa protein mainly produced and secreted by white adipose tissue and informing various brain centers via leptin receptor long and short forms about the amount of fat stored in the body. In this way leptin exerts a plethora of regulatory functions especially related to energy intake and metabolism, one of which is controlling the activity of the hypothalamo-pituitary–adrenal (HPA) stress axis. First, this review deals with the basic properties of leptin's structure and signaling at the organ, cell and molecule level, from lower vertebrates to humans but with emphasis on rodents because these have been investigated in most detail. Then, attention is given to the various interactions of adipose leptin with the HPA-axis, at the levels of the hypothalamus (especially the paraventricular nucleus), the anterior lobe of the pituitary gland (action on corticotropes) and the adrenal gland, where it releases corticosteroids needed for adequate stress adaptation. Also, possible local production and autocrine and paracrine actions of leptin at the hypothalamic and pituitary levels of the HPA-axis are being considered. Finally, a schematic model is presented showing the ways peripherally and centrally produced leptin may modulate, via the HPA-axis, stress adaptation in conjunction with the control of energy homeostasis.

1. Introduction

1.1. The leptin protein

Studying their in-house mouse breeding data, Ingalls et al. [60] noticed that 43 mice out of an offspring of 212 animals had an obese, hyperphagous, hyperglycemic and infertile phenotype, approximating the 1:3 ratio of a simple recessive gene, which they called the *obese* gene (*ob*). Coleman [23], connecting the circulation of the homozygote (*ob/ob*) mutant with that of a wild-type mouse, found that the obese mutant ate less and lost weight whereas the wild-type mouse remained lean, which suggested the existence of a blood–borne factor in the wild-type mouse that inhibited food intake. Zhang et al. [136] revealed that the mouse *ob* gene encodes a 4.5 kb mRNA transcript that gives rise to a 16-kDa protein they called leptin, after the Greek *leptos* for 'thin'. Upon injection with leptin, *ob/ob* mice lose excess fat and return to normal body weight [54]. The mouse *ob* gene is located on chromosome 6, and that of human on chromosome 7q31.3. Leptin DNA consists of 15,000 base pairs, which form three exons and two introns. Human leptin has 167 amino acid residues and structurally closely resembles mouse and rat leptin [21,109]. Leptin's strong evolutionary conservation, indicating its functional importance, appears from the presence of orthologs of the mammalian *ob* gene in reptiles and amphibians [34], birds [65] and fish [49]. Mutations of the *ob* gene lead to hyperphagy and severe obesity in both animals and humans, underlining leptin's strong inhibitory effect on food intake [86,94]. Most leptin is synthesized in adipocytes of white adipose tissue (WAT), and the titer of circulating leptin is directly proportional to the total amount of body WAT [102]. Other sources of leptin are brown adipose tissue (BAT), placenta, ovaries, skeletal muscle, stomach, mammary epithelial cells, bone marrow, pituitary gland, liver and the brain; for reviews, see Refs. [81,87].

1.2. Leptin actions, receptors and targets

Leptin has pleiotropic effects, playing a key role in physiology by controlling various aspects of energy intake and expenditure, such as centrally inhibiting appetite, suppressing lipogenesis, modulating T-cell activity and the mammalian ovulatory cycle, promoting angiogenesis and surfactant expression in type II pneumocytes, regulating bone metabolism and inflammatory responses and influencing via the hypothalamo-pituitary–adrenal (HPA-) axis the stress response, e.g., [12,15,80].

In order to understand the central and local mechanisms by which leptin exerts this plethora of functions, much research has been performed on the central and peripheral distributions of

* Corresponding author.
E-mail address: roubos@science.ru.nl (E.W. Roubos).

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leptin receptors. Parabiosis experiments revealed that the high body weight of diabetic *db*/*db* mice was not normalized when these mice were connected to lean wild-type mice, suggesting that *db*/*db* mice are defective in their ability to respond to leptin [24]. The *db* gene, which causes obesity, was shown on chromosome 4, and turned out to be identical with the leptin receptor gene cloned by Tartaglia et al. [115]. Using a murine choroid plexus cDNA library, the cell surface leptin receptor ObR, commonly referred to as LepRb, was identified. LepRb appeared to be a glycoprotein containing a single transmembrane-spanning component with intracellular motifs necessary for signal transduction [2] and with docking sites for members of the Janus kinase (JAK) family of tyrosine kinases [114]. Upon leptin binding, activated JAK phosphorylates intracellular signal transduction and transcription (STAT) proteins that, in turn, stimulate transcription of target genes to mediate cellular leptin effects [104]. Further screening of the mouse cDNA library revealed in addition to the LepRb long form, five LepR short forms (LepRa-f) [1,72]. The six isoforms share the extracellular leptin-binding domain typical for class I cytokine receptors but differ from each other at the carboxyterminal intracellular domain [2,55] (Fig. 1).

LepRs occur in several peripheral organs, such as the heart, liver, lung, ovaries, pituitary gland, endocrine pancreas, skeletal muscle, testis and hemopoietic organs (for reviews, see Refs. [32,43]) and, remarkably, in adipose tissue, where leptin binding to LepRb activates the JAK/STAT pathway, increasing glucose utilization and lipolysis, as shown in rat [106]. Mouse studies revealed that leptin also acts directly on adipocytes, to control rosiglitazone-induced adipocyte differentiation and peroxisome proliferator-activated receptor PPAR-γ expression, via JAK/STAT and extracellular signal-regulated kinases/mitogen-activated protein kinase (ERK1/2-MAPK) signaling pathways [98].

Of particular interest in the present context is the action of leptin on LepR in several endocrine cell types of the rat [108], ovine [61], bovine [91] and human [46,47] anterior pituitary and adrenal glands, and at various sites in the brain, such as in the choroid plexus, the ventral tegmental area, the arcuate (ARC) and paraventricular nuclei (PVN), and the ventromedial and dorsolateral hypothalamus, as shown in rodent binding, immunohistochemical and *in situ* mRNA hybridization studies, e.g., [38,41,51,93]. The fact that intracerebroventricular (icv) administration of leptin in mice reduces food intake and induces weight loss indicates that leptin can act directly on LepR in the central nervous system, informing various parts of the brain about the amount of peripherally stored energy, e.g., [18,50].

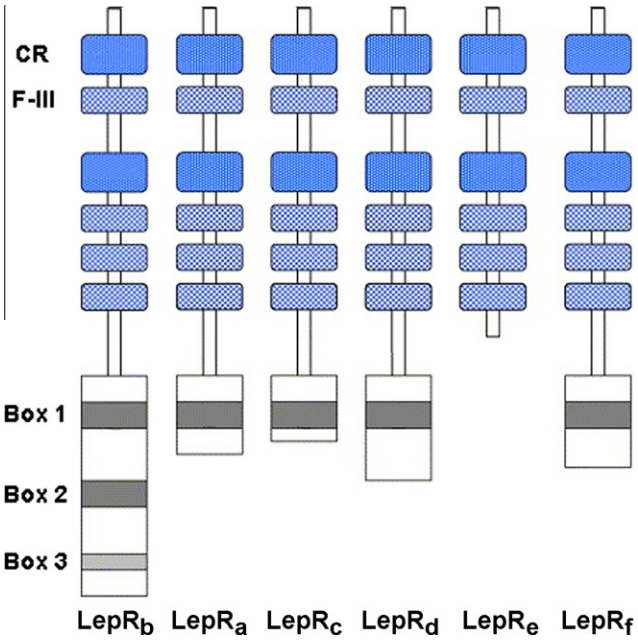

Fig. 1. Structure of the six alternatively spliced leptin receptor isoforms ($LepR_{a-f}$). The extracellular leptin-binding domain is similar in all isoforms but each isoform has a specific carboxyterminal intracellular domain. Boxes 1, 2, 3, consensus intracellular motifs; CR, cytokine receptor domain; F-III, fibronectin type III domain (modified from Ref. [55]).

1.3. Leptin transport into the brain

Leptin circulates at a level proportional to the amount of stored body fat, enters the brain in proportion to its plasma concentration, and controls food intake and energy expenditure by acting on its hypothalamic receptors [127]. As leptin is mainly produced peripherally, in the adipose tissue, it needs to cross the blood–brain barrier (BBB) to be able to act inside the brain. By injecting ^{125}I-leptin into mice, Banks et al. [7] demonstrated unidirectional transport via a saturable system of intact leptin from blood to brain. The short receptor form LepRa plays a role in this transport [64] but Koletsky strain rats, which lack this receptor isoform, do reveal leptin influx into the brain, which suggests the additional involvement of another leptin receptor isoform in trans-BBB leptin transport [64]. The precise nature of the leptin transport mechanism still being unrevealed, it is generally assumed that leptin is transported across the BBB via LepRs that are located in nonneuronal cells in the meninges, choroid plexus and blood vessels [96]. Furthermore, soluble LepRe circulating in the blood, appears to act as an antagonist of LepRb-stimulation of leptin transport across mouse endothelial cells [116].

1.4. Leptin production in the brain

Although adipose tissue-derived messengers like leptin have received little attention as brain-derived putative neuromodulators of energy balance, there is evidence for leptin production in the rodent brain, e.g., [13,14,125]. Since women and obese men have a higher concentration of leptin in the internal jugular vein than in the arterial blood, Wiesner et al. [124] proposed that leptin is released from the brain into the blood, suggesting the presence of an intrinsic brain source of leptin. Subsequently, the presence of leptin and its mRNA in rat brain was inferred from leptin immunocytochemistry and PCR studies, respectively [87,126], and later leptin mRNA was detected in the brain of several other mammalian species, including rodents, sheep, pig and human, though not in mice [9,36,63,137]. Recently, leptin expression was shown by PCR and immunocytochemistry in the rat medial preoptic area and in the hypothalamic ARC and dorsomedial nuclei, confirming that the protein is produced in areas related to feeding behavior [31].

Regulation of brain leptin mRNA by fasting was shown in the rat ARC [87] and more recently *ob* gene expression in the rat hypothalamus was found to be down-regulated by prolonged food restriction similarly as in WAT, whereas in contrast to WAT this downregulation could not be abolished by refeeding. These observations indicate that prolonged fasting/refeeding affects *ob* gene expression in the hypothalamus differently from that in adipose tissue [111]. Possibly, brain-derived leptin acts in local regulatory brain circuits that fine-tune and/or complement the negative feedback of adipose tissue-derived leptin on the control of energy homeostasis [125]. In this review, we will consider one aspect of this control in detail, viz. the possible and the confirmed actions of peripherally as well as centrally produced leptin on the central stress adaptation system, the HPA-axis.