Leptin and Hormones
Energy Homeostasis

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KEYWORDS

• Leptin • Energy homeostasis • Metabolism • Hormonal interactions • Obesity

KEY POINTS

- Leptin is a 167 amino acid adipokine; its interaction with the leptin receptor activates mainly the Janus kinase (JAK)–signal transducer and activator of transcription 3 (STAT3) signal transduction pathway.
- Leptin's primary action site is the central nervous system, especially the hypothalamus.
- Energy deprivation conditions, such as hypothalamic amenorrhea (HA) and lipodystrophy, are characterized by low leptin levels.
- Obesity is usually characterized by hyperleptinemia, but the hypothalamus is resistant or tolerant to the effects of increased leptin, except for the rare condition of congenital leptin deficiency due to leptin gene mutation.
- Leptin replacement treatment improves, and even normalizes, most of the endocrine and metabolic abnormalities in patients who suffer from conditions characterized by low leptin levels, such as lipodystrophy, HA, and congenital leptin deficiency.

INTRODUCTION

Leptin is an adipokine and its name derives from the Greek word λεπτός (*leptos*), which means thin. Since its initial discovery in 1994, important advances have been made, and human recombinant leptin is currently available and approved for pharmacologic use.[1–4] This article reviews the role of leptin in energy homeostasis. Specifically, the structure, production, and signaling of leptin are described first, followed by its action at both central and peripheral levels. Then, the role of leptin in conditions of energy deprivation or excess is discussed, along with leptin's existing and potential future therapeutic applications.

Disclosure Statement: The authors have nothing to disclose.
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Endocrinol Metab Clin N Am 45 (2016) 633–645
http://dx.doi.org/10.1016/j.ecl.2016.04.012 **endo.theclinics.com**
0889-8529/16/$ – see front matter

STRUCTURE, PRODUCTION, AND SIGNALING OF LEPTIN

Leptin is a 167 amino acid protein folded in a 4-helix bundle structure, which is produced by the expression of the *lep* gene.[5,6] It is expressed mainly in the white adipose tissue.[7] This is an approximately 20-kb gene located on chromosome 7, containing 3 exons separated by 2 introns.[8,9] In humans, leptin is secreted in a pulsatile fashion, with the highest levels present in the blood during evening hours, a pattern opposite to that of corticotropin and cortisol.[10] The total concentration of leptin is directly proportional to total body fat mass.[11] Its actions (discussed later) are mediated through binding to the leptin receptor, a single transmembrane-spanning protein,[12] member of the class I cytokine receptor family.[13] Several isoforms of that receptor exist, which are produced after alternate mRNA splicing.[14,15] One of them, the lep-Re isoform (soluble leptin receptor), represents the major leptin binding protein in the plasma.[16,17] The long leptin receptor isoform mediates signal transduction and is strongly expressed in the hypothalamus.[18]

The leptin-leptin receptor interaction activates mainly the JAK-STAT3 signal transduction pathway, which is the most important regulator of energy homeostasis.[19–21] Secondarily, the following pathways can be also activated: (1) phosphatidylinositol 3-kinase, which is important for regulation of both food intake and glucose homeostasis[22]; (2) mitogen-activated protein kinases/extracellular signal-regulated kinases pathway, which plays a role in fatty acid synthesis regulation[23]; (3) 5′-adenosine monophosphate–activated protein kinase, a potential coregulator pathway of pancreatic β-cell functions and insulin secretion[24]; and (4) mammalian target of rapamycin, a pathway that seems to promote intestinal cell proliferation.[25]

Signaling of leptin in peripheral blood mononuclear cells seems to reflect its signaling in other metabolically important tissues, such as muscle and adipose tissue.[26,27] A recent study conducted by the authors' group in obese women showed that 10% to 15% weight loss resulted in a decrease in leptin levels, in parallel with a decrease in baseline STAT3 phosphorylation of their peripheral blood mononuclear cells. Ex vivo treatment of those PMBCs with supraphysiologic leptin doses significantly increased extracellular signal–regulated kinase, STAT3, and protein kinase B phosphorylation. The phosphorylation levels of those proteins were higher after administration of supraphysiologic doses compared with either physiologic doses or no treatment.[28] Further studies are needed to elucidate the molecular pathways triggered by leptin as well as the potential therapeutic benefits that could derive from their manipulation.

CENTRAL ACTION OF LEPTIN

After its secretion from adipocytes, leptin circulates in the blood bound to lep-Re, acting as a marker of total body energy stored in fat and secondarily as marker of acute changes in energy intake.[29–31] It gets transferred through the blood-brain barrier via the short leptin receptor isoform to the hypothalamus, where it mediates most of its actions.[32–35] More specifically, it acts on the supraoptic nucleus, paraventricular nucleus, periventricular nucleus, arcuate nucleus, and lateral hypothalamus.[34,35] There, it interacts with a complex circuit, activating neurons that synthesize anorexigenic peptides, namely pro-opiomelanocortin (POMC)[36] and cocaine- and-amphetamine-regulated transcript (CART).[37] At the same time it suppresses the activity of orexigenic neurons, which express agouti-related peptide (AgRP) and neuropeptide Y (NPY).[38–40] Leptin's action at the hypothalamus is also responsible for counterbalancing the effect of ghrelin, which is a major orexigenic hormone.[41,42] In addition to the hypothalamus, leptin acts on the mesolimbic dopamine system, which is part of the brain reward