Leptin – part 2

Mary ET Boyle
Leptin Feedback:

• leptin levels drop during starvation,
• when fat depots are depleted to support the organism’s basic energy needs,
• leptin levels rise during refeeding
• where fat depots are replenished.
Leptin aka “ob protein”

16 kDa protein encode ob gene

ob/ob mice
Leptin deficient

1994
Jeffrey Frieman

Strong leptin expression in white adipose tissue (WAT)

and elsewhere...
Brown Adipose Tissue (BAT)

Placenta
The placenta is an important source of leptin.
Skeletal muscle

Weight loss does not always accompany leptin reduction

Recall, leptin is a mediator of fat-brain cross-talk with nutrient status

Skeletal muscle – largest metabolically active organ

Cultured myocytes are capable of producing and releasing leptin

Hyperglycemia and hyperlipodemia induce leptin release in myocytes

Should leptin be a myokine?
Fundic glands of the stomach

In addition to leptin synthesis, epithelial cells may transfer leptin from the blood, and these two mechanisms may account for the presence of leptin in the milk.

Bone Marrow

- Leptin/LepR signaling regulates osteogenesis by skeletal stem cells in bone marrow.
- LepR signaling promotes adipogenesis and inhibits osteogenesis by BM stromal cells.
- A high-fat diet promotes BM adipogenesis through LepR signaling in BM stromal cells.
- LepR signaling in bone marrow mesenchymal stromal cells inhibits fracture healing

Leptin is stored in pituitary secretory granules and secretory cells retain leptin in granules until stimulated.

“Subcellular localization of leptin indicates co-storage with secretory granules and implicates hypothalamic releasing hormones in leptin secretion from anterior pituitary hormone cells. Leptin signal transduction in the anterior pituitary has been shown to involve the janus protein-tyrosine kinase (JAK)/signal transducer and activation of transcription (STAT) as well as suppressor of cytokine signalling (SOCS). These proteins are activated by tyrosine-phosphorylation in anterior pituitary cells.”

growth hormone (GH), prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), and thyroid-stimulating hormone (TSH)
FIGURE 1. Hexagonal crystals of leptin-E100 protein. Wild-type leptin aggregates severely and is resistant to crystallization. A single amino acid replacement of 100 Trp to Glu yielded a soluble analog that readily crystallized.
Self association and aggregation of Leptin:

- It consists of four antiparallel a-helices (A, B, C, and D),
- connected by two long crossover links (AB and CD),
- and one short loop (BC), arranged in a left-hand twisted helical bundle.
- Hydrophobic residues \(\rightarrow\) receptor binding

leptin has a striking structural similarity to other long-chain helical cytokines
FIGURE 2. Crystal structure of leptin. (a) Ribbon diagram of the four-helical conformation. Four helixes take an up-up-down-down arrangement, with a small helix E in the CD loop. The 100 Trp position was shown as a red CPK model on the surface of the molecule. (b) The surface structure of leptin. Blue is for N, red for O, and white for C atoms. Hydrophobic residue side chains are in white. With the exception of Trp100, other hydrophobic residues like Phe 92, Leu142, Trp138, and Phe 41 are also located on the surface.
**Leptin Receptor**

| In 1995, Louis Tartaglia and colleagues identified the leptin receptor gene in the db locus of mouse chromosome 4 | class I cytokine receptor superfamily | Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signal transduction pathway |
| At least five isoforms from alternate splicing | OBRa, OBRb, OBRc, OBRd, and OBRe | All leptin receptors share an identical N-terminal ligand-binding domain but diver at the C-terminal region. |
OBRa, OBRb, OBRc, and OBRd receptor isoforms contain a single transmembrane region, whereas the OBRe receptor is truncated proximal to the membrane-spanning domain. OBRe isoform without a membrane anchor functions as a soluble circulating leptin-binding protein.

Expressed in most tissues

OBRb only one that can has full signal transduction

OBRb is responsible for energy homeostasis and feeding
Schematic view of OBR protomer

- Immunoglobulin domain
- Fibronectin III domain
- Cytokine receptor homology domains
- Transmembrane region

Box 1 motif known to bind JAK kinases
Box 2 motif is required for STAT signaling

(CRH)2 is the main binding site for leptin

Image adapted from: https://mutagenetix.utsouthwestern.edu/phenotypic/phenotypic_rec.cfm?pk=109
OB-Rb

- Obesity related
- Hypothalamus
- Ob/ob and db/db
- Hyperphagia and obesity
Leptin: signals satiety (arcuate n.) regulates thermogenesis, bone formation, and reproductive function in hypothalamus.

In the hippocampus, exposure to leptin enhances activity-dependent plasticity via NMDA receptors and morphological changes of the neurons.

Harvey, J (2015)
SLR – soluble leptin receptor – OB-Re

- **OB-Re**
  - CRH1
  - IG-like
  - CRH2
  - FNIII

- **Binds in plasma**
- **Leptin clearance**
- **Regulating plasma levels of active leptin**

- **Feedback relationships:**
- **Plasma Leptin:** Direct relationship with BMI
- **SLR:** Indirect/inverse with BMI
Leptin Signaling

- IL-6 receptor family
- Class I cytokine receptors
- Extracellular binding domain
- Transmembrane domain
- Cytoplasmic signaling domain

(Interleukin)
Leptin signaling via JAK-STAT pathway

JAK - Janus Kinase

STAT - Signal Transducers & Activators of Transcription

Receptor OB-Rb
leptin receptor

OB-Rb

membrane

intracellular binding domain

JAK

Janus Kinase
2. The associated JAKs are brought together when leptin binds. Leptin binds JAKs phosphorylate each other on their tyrosines to become activated.
once activated, they can phosphorylate the receptor to generate binding sites for the SH2 domains of STAT proteins.
* SH2 domains of STAT proteins bind
* the activated JAK $\text{P}$ STAT protein
STAT is released and forms a dimerization
once dimerized,

\[
\text{ STAT Translocates into the nucleus}
\]

binds to DNA promoter region

DNA

nucleus
Summary

JAK

STAT

Pathway

Leptin

Receptor (OB-Rb)

Nucleus

DNA

Specific gene transcription
How does Leptin’s JAK-STAT pathway affect feeding behavior?

Leptin binds to OB-Rb:

- STAT3 binds to the POMC promoter
- POMC is precursor to α-MSH
- α-MSH is a MC4R agonist

Leptin inhibits food intake.

Mutations in POMC and MC4R genes lead to severe obesity in rodents and humans. Deletions of STAT3 leads to hyperphagia and obesity.

POMC: proopiomelanocortin - anorectic neuropeptide
α-MSH: α-Melanocyte-stimulating hormone
MC4R: melanocortin 4 receptor
“SOCS3 is an SH2 domain-containing protein that can bind phosphorylated Tyr985 LRb to mediate inhibition of LRb–STAT3 signaling”
OB-Rb mRNA is expressed most highly in ARC, where it is found in at least two distinct populations of neurons. One population synthesizes neuropeptide Y (NPY) and agouti-related peptide (AgRP) and the other synthesizes pro-opiomelanocortin (POMC).

POMC is processed to produce the powerful anorectic (appetite suppressing) peptide α-melanocyte-stimulating hormone (αMSH) in OB-Rb/POMC neurons.

AgRP inhibits αMSH signaling and NPY is an orexigenic (appetite-stimulating) hormone.

Leptin stimulates the production of anorectic neuropeptides and suppresses levels of orexigenic peptides.
Model of leptin regulation of neurons expressing neuropeptide Y and agouti-related protein (NPY/AgRP neurons) and proopiomelanocortin (POMC neurons) in the arcuate nucleus of hypothalamus (ARH).

Figure from: Jobst, et al. (2004)
Lateral
Medial
Periventricular
Third ventricle

Hypothalamus
OB-Rb is present in several tissues, with the highest levels in neurons of the nuclei of the basomedial hypothalamus, including the arcuate (ARC), dorsomedial hypothalamic (DMH) and ventromedial hypothalamic (VMH) nuclei.
Review

Leptin receptor action and mechanisms of leptin resistance

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New pharmacological perspectives for the leptin receptor in the treatment of obesity

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Leptin and Alzheimer’s Disease

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Leptin Receptor Promotes Adipogenesis and Reduces Osteogenesis by Regulating Mesenchymal Stromal Cells in Adult Bone Marrow

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The stomach is a source of leptin


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Effects of maternal obesity on early and long-term outcomes for offspring

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Abstract: The prevalence of maternal obesity has increased significantly in recent years, and
obesity is currently the most common comorbidity of pregnancy. Pregnancies of obese women
are often defined as “high-risk” for the purposes of clinical care, with many well documented
risks to the mother and developing baby. Maternal physiology and metabolism is dysregulated in
the context of obesity, which may contribute to some of the adverse outcomes during pregnancy.
Furthermore, maternal obesity has been hypothesized to cause harmful effects for the developing
baby through “early life programming.” This review will examine evidence from human studies for outcomes of offspring from obese women during pregnancy, during labor, during
the neonatal period, and later in life.

Keywords: pregnancy, short-term, physiology, metabolism, early life programming, neonatal
complications, adverse intrauterine environment
Unexpected evidence for active brown adipose tissue in adult humans
Jan Nørgaard, Tore Bengtsson, Barbara Cannon
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Three years with adult human brown adipose tissue
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Human skeletal muscle releases leptin in vivo

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Neurobiology of Feeding and Energy Expenditure

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The role of leptin receptor signaling in feeding and neuroendocrine function

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The electrophysiology of feeding circuits

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Review

Obesity and leptin resistance: distinguishing cause from effect

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