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

- Leptin aka “ob protein”
- ob/ob mice, Leptin deficient
- 16 kDa protein encode ob gene
- Strong leptin expression in white adipose tissue (WAT)
- 1994 Jeffrey Frieman
- and elsewhere...
Brown Adipose Tissue (BAT)

Placenta
The placenta is an important source of leptin.

Sirrat & Reynolds (2014)
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

Mammary epithelial cells

“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.”
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 \( \alpha \)-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.
In 1995, Louis Tartaglia and colleagues identified the leptin receptor gene in the db locus of mouse chromosome 4.

At least five isoforms from alternate splicing.

Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signal transduction pathway.

All leptin receptors share an identical N-terminal ligand-binding domain but diVer at the C-terminal region.

- OBRa, OBRb, OBRc, OBRd, and OBRe

Class I cytokine receptor superfamily.
| OBRa, OBRb, OBRc, and OBRd receptor isoforms contain a single transmembrane region, |
| OBRb only one that can has full signal transduction |
| OBRb is responsible for energy homeostasis and feeding |

- OBRa, OBRb, OBRc, and OBRd receptor isoforms contain a single transmembrane region, whereas the OBRre receptor is truncated proximal to the membrane-spanning domain.
- OBRre isoform without a membrane anchor functions as a soluble circulating leptin-binding protein.
- 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
- Transmembrane region
- Cytokine receptor homology domains

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

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.

Leptin Receptor Expression in CNS:

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

- **OB-Re**
  - 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

(Interleukin)
IL-6 receptor family

Class 1 cytokine receptors

\{ extracellular binding domain \}

\{ transmembrane domain \}

\{ cytoplasmic signaling domain \}
Leptin signaling via JAK-STAT pathway

JAK - Janus Kinase

STAT - Signal Transducers & Activators of Transcription

family of tyrosine kinases

Receptor DB-Rb
leptin receptor

DB-Rb

membrane

intracellular binding domain

JAK

Janus Kinase
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 P STAT protein
STAT is released and forms a dimerization
once dimerized,

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

DNA

binds to DNA promoter region

nucleus
Summary

JAK

JAK/STAT Pathway

Leptin Receptor (OB-Rb)

Nucleus

DNA

Specific gene transcription
Review

Leptin receptor action and mechanisms of leptin resistance

H. Münzberg, M. Björnholm, S. H. Bates and M. G. Myers Jr*

Division of Metabolism, Endocrinology and Diabetes, Departments of Internal Medicine and Molecular and Physiology, University of Michigan Medical School, 1150 W. Medical Center Dr., 4301 MSRB 3, Box 0638, Ann Arbor, Michigan 48109-0638 (USA), Fax: +1 734 936 6684, e-mail: mgmyers@umich.edu

Received 30 September 2004; received after revision 12 November 2004; accepted 23 November 2004

1420-682X/05/060642-11
DOI 10.1007/s00018-004-4432-1
© Birkhäuser Verlag, Basel, 2005
REVIEW ARTICLE

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

Clara Roujeau¹,²,³, Ralf Jockers¹,²,³ and Julie Dam¹,²,³*

¹INSERM, U1016, Institut Cochin, Paris, France
²CNRS UMR 8104, Paris, France
³University of Paris Descartes, Sorbonne Paris Cité, Paris, France
Leptin and Alzheimer’s Disease

Jenni Harvey, BSc, PhD
University of Dundee, Dundee, Tayside, UK

Diet and Nutrition in Dementia and Cognitive Decline.
© 2015 Elsevier Inc. All rights reserved.
Leptin Receptor Promotes Adipogenesis and Reduces Osteogenesis by Regulating Mesenchymal Stromal Cells in Adult Bone Marrow

Rui Yue, Bo O. Zhou, Issei S. Shimada, Zhiyu Zhao, and Sean J. Morrison

1Howard Hughes Medical Institute
2Department of Pediatrics and Children’s Research Institute
University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
*Correspondence: sean.morrison@utsouthwestern.edu
http://dx.doi.org/10.1016/j.stem.2016.02.015

http://dx.doi.org/10.1016/j.stem.2016.02.015
The stomach is a source of leptin


* Institut National de la Santé et de la Recherche Médicale (INSERM) Unité 10, IFR2 Cellules Epithéliales, Hôpital Bichat, 170 boulevard Ney, 75018 Paris, France
‡ INSERM U145, Faculté de Médecine, avenue de Valombrose, 06107 Nice, France
§ INSERM U465, Institut des Cordeliers, 15, rue de l’Ecole de Médecine, 75006 Paris, France
† These authors contributed equally to this work
Effects of maternal obesity on early and long-term outcomes for offspring

Laura I Stirrat1,2
Rebecca M Reynolds1,3

1Medical Research Council Centre for Reproductive Health, Queens Medical Research Institute, University of Edinburgh, Edinburgh, UK; 2Tommy’s Centre for Maternal and Fetal Health, Queens Medical Research Institute, University of Edinburgh, Edinburgh, UK; 3Endocrinology Unit, University of Edinburgh, British Heart Foundation Centre for Cardiovascular Science, Queens Medical Research Institute, University of Edinburgh, Edinburgh, UK

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 Nedergaard, Tore Bengtsson, Barbara Cannon
American Journal of Physiology - Endocrinology and Metabolism Published 31 July 2007 Vol. 293 no. 2, E444-E452 DOI: 10.1152/ajpendo.00691.2006

Three years with adult human brown adipose tissue

Jan Nedergaard, Tore Bengtsson, Barbara Cannon
First published: November 2010 Full publication history
Human skeletal muscle releases leptin in vivo

Emil Wolsk a,*, Helene Mygind a, Thomas S. Grøndahl a,b, Bente K. Pedersen a, Gerrit van Hall a,b,c

a The Centre of Inflammation and Metabolism, Department of Infectious Diseases and CMRC, Rigshospitalet, Faculty of Health Sciences, University of Copenhagen, Denmark
b Metabolic Mass Spectrometry Lab, Rigshospitalet, Faculty of Health Sciences, University of Copenhagen, Denmark
c Department of Biomedical Sciences, Faculty of Health Sciences, University of Copenhagen, Denmark