Leptin – Master Appetite Modulator

TO EAT OR NOT TO EAT...
Controls food intake

Hypothalamus

Produced in fat cells

Metabolic state of the body
Structure of the Human Obesity Receptor Leptin-Binding Domain Reveals the Mechanism of Leptin Antagonism by a Monoclonal Antibody

Byron Carpenter¹, ², Glyn R. Hemsworth², Zida Wu³, Mabrouka Maamra¹, Christian J. Strasburger³, Richard J. Ross¹, ², Peter J. Artymiuk², ³.

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1. produced in fat cells
2. informs brain of current metabolic state
3. Neurons & effects

FAT CELLS

- Leptin

Hypothalamus

Communicates to hypothalamus
Leptin and the Central Nervous System Control of Glucose Metabolism

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Mary ET Boyle, Ph. D.
Department of Cognitive Science
UCSD
Hormonal signals produced in proportion to body fat stores act centrally to form a negative feedback loop to maintain HOMEOSTASIS.
NOTE: ADIPOSE TISSUE

IS AN ENDOCRINE ORGAN
→ COMMUNICATES W/ BRAIN & PERIPHERY

SECRETES HORMONES THAT REGULATE

① APPETITE
② METABOLISM
Leptin functionality is dependent on 4 factors:

1. Location: visceral vs. subcutaneous
2. Size: large vs. small
3. Adipocyte metabolism of glucose
4. Cortico-steroids
Leptin information about long-term energy stores

Energy stores & nutrient availability
- Leptin
- All about food consumed relative to energy
- Expended

Long-term
- Glucose
- FFA
- Body temperature
- Plasma amino acids
- CO2

Short-term

Food intake meter
- Hunger
- Satiety

Eat food

Energy expenditure

Periphery
- Glucose uptake

Insulin sensitivity
- Glucose production
- Endogenous glucose production
Leptin & Insulin

INFO ABOUT LONG-TERM ENERGY STORES

INFO ABOUT SHORT-TERM ENERGY AVAILABILITY

GLUCOSE & FREE FATTY ACIDS
Reduced energy stores

- Yes
  - Need to promote positive energy balance

- No
  - Nutrient abundance & excess energy storage
Reduced energy stores

Nutrient abundance & excess energy storage

1. Promote negative energy balance
2. Limit endogenous glucose production
Reduced energy stores

- Need to promote positive energy balance
- Increase food intake
- Reduce energy expenditure
- Increase nutrient availability: endogenous glucose production
- Fat metabolism
Availability of Energy Stores

- **Positive Energy Balance**
- **Negative Energy Balance**

- **Eat**
- **Energy**
- **Glucose**

**Energy Balance**
- Red: Food Intake
- Blue: Energy Expenditure
- Green: Endogenous Glucose Production
**Leptin Facts**

1. Plasma levels of leptin are correlated with adipose tissue mass.

   - Adipose mass \( \rightarrow \) Leptin \( \rightarrow \) Leptin in plasma
   - Peripheral effects
     - \( \beta \) cells
     - \( T \) cells

2. Expressed in adipose tissues, gastric epithelium, placenta (highest levels).

   - Behavioral changes
     - \( \uparrow \) leptin \( \Rightarrow \) negative energy balance
     - \( \downarrow \) leptin \( \Rightarrow \) positive energy balance

   - (Energy expenditure > Food intake)
   - (Food intake > Energy expenditure)

   - Decreased plasma levels of leptin signal nutrient deprivation.
2. Injection of leptin into plasma:
   - Reduction of body weight (close dependent !!)
   - Adipocytes mass decreased
   - No change in lean muscle mass

\[ \text{Injection of physiological levels} \]
③ **LEPTIN LEVELS**

- Do not change significantly after meals
- Does not cause meal termination (by itself)

**“LONGTERM” SIGNAL**
NO LEPTIN

DB/DB MICE LACK LEPTIN RECEPTOR & HAVE SAME PHENOTYPE AS 06/06

06/06 MICE EXHIBIT THE SAME EFFECTS SEEN IN STARVED ANIMALS -

- ↓ DECREASED BODY TEMPERATURES
- ↓ DECREASED ENERGY EXPENDITURE (↓ ACTIVITY)
- ↓ DECREASED IMMUNE FUNCTION
- ↓ FOOD CONSUMPTION (HYPERPHAGIA)
- LEADS TO OBESITY IN THE PRESENCE OF FOOD

RETTEVED STARVATION

- INFERTILITY
- THYROID & CORTECOSTERONE HORMONES ARE AFFECTED BY LEPTIN LEVELS

LEPTIN STIMULATES PROLIFERATION OF CD4+ T CELLS & PRODUCTION OF CYCLOXINSE BY T-HELPER-1 CELLS

- LEPTIN LINKS NUTRITIONAL STATE & THE IMMUNE SYSTEM

LEPTIN REGULATES ONSET OF PUBERTY (♀ ESTROUS CYCLE)

WHEN LEPTIN IS REPLACED IN 06/06 MICE, THESE ABNORMALITIES GO AWAY.
Leptin acts centrally by:

- inhibiting appetite

\[ \uparrow \text{decreasing activity of orexigenic neurons} \]
\[ \downarrow \text{NPY, AgRP, GABA} \]

\[ \uparrow \text{increasing activity in anorexigenic neurons} \]
\[ \text{POMC, CART} \]

Key:
- orexigenic:
  - eat
- anorexigenic:
  - no eat

Diagram:
- Hypothalamic nuclei
  - arcuate nucleus
  - dorsal medial
  - paraventricular nucleus

Leptin receptor LEPRb
**Leptin**

- Response to obesity
- Gain weight
- Leptin

- Activation of NPY orexigenic pathways
- Increase in food intake and energy expenditure
- Normal sympathetic tone

- Activate andorexigenic pathways
- Decrease in food intake and energy expenditure
- Increase in sympathetic tone

Response to starvation

Positive energy balance
LEPTIN DYSREGULATION

1. NO LEPTIN PRODUCED $\Rightarrow$ OBESITY

   $ob/ob$ $\Rightarrow$ no leptin
   $\Rightarrow$ CONSTANT STARVATION SIGNAL
   $\Rightarrow$ PROMOTE POSITIVE ENERGY BALANCE
   $\downarrow$ FOOD INTAKE
   $\downarrow$ ENERGY EXPENDITURE
   $\uparrow$ NUTRIENT AVAILABILITY (FAT/GLUCOSE)
LOW LEPTIN SECRETION
FOR A GIVEN FAT MASS

the amount of leptin produced is equivalent to

ACTUAL FAT MASS

this leads to signals that will increase fat mass so the result would be:

overeating.
LEPTIN INSENSITIVITY

1. db/db phenotype
   - absolute insensitivity
   - no matter the [leptin] plasma
   - the signals are muted
   - that there is not
   - enough leptin
   - result is to promote
     POSITIVE ENERGY BALANCE
   - ↑ food intake
   - ↓ energy expenditure
   - ↑ nutrient available (fat/sucrose)
   - => obesity

2. Leptin Receptor unsensitivity/resistance
   - similar to db/db but
   - not as severe.
   - ↓ high levels of leptin in
     plasma
Figure 2
Effects of r-metHuLeptin therapy on energy intake. (a) Energy intake at an ad libitum test meal before (black bars) and 2 months after (white bars) r-metHuLeptin therapy in child A, B, and C. Energy intake (KJ) expressed per kilogram lean body mass to compare intake of subjects of different age and body size. (b) Changes in body mass index SDS (BMI SDS) (filled symbols) and energy intake at an 18-MJ ad libitum test meal (gray bars) during 36 months of treatment in child B. Panels indicate duration of r-metHuLeptin dose expressed as a percentage of predicted serum leptin concentration based on age, gender, and body composition.
Weight curve for the proband compared with normal percentiles for girls. Initiation of leptin therapy is marked by an arrow.

Table 1. Summary of the effects of leptin replacement therapy

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<td>Decrease in triglycerides and increase in high-density lipoprotein cholesterol (HDL-C)</td>
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<td></td>
<td>Inhibition of lipogenesis and stimulation of lipolysis</td>
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<tr>
<td>Biomarkers of inflammation, coagulation, fibroinhibins and platelet aggregation</td>
<td>Leptin withdrawal, changes towards a decreased state of thrombogenesis and increased fibrinolysis</td>
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<td>Immunity</td>
<td>Decrease in the absolute lymphocyte count (CD8, CD4, CD19 cells)</td>
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<td>Increased T-cell responsiveness[a]</td>
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</table>

[a] Alterations assessed exclusively in patient D.

Our results are important not only to guide the treatment of leptin-deficient patients — including those with lipodystrophy syndromes, but also to direct future studies on the usefulness of leptin in treating or preventing other diseases or conditions, such as common obesity, lipodystrophy syndromes, diabetes, hypothalamic amenorrhea, anorexia nervosa, mood and cognitive disorders, immune deficiencies and lipodystrophy.

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<th>Anti-obesity treatment?</th>
<th>Exogenous leptin treatment for obese patients was unsuccessful...</th>
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<td>Why?</td>
<td>Already had high levels of leptin in plasma circulation</td>
</tr>
<tr>
<td>Leptin no longer worked</td>
<td>Leptin resistance was the problem, not lack of leptin</td>
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Congenital leptin deficiency

- Administration of recombinant leptin
- Decrease body weight

Diet Induced Obesity

- Administration of leptin is ineffective
- Hyperleptinemic with a loss of leptin responsiveness
“The brain continuously transduces input from neural, hormonal, and nutrient-related signals into responses that maintain both energy and glucose homeostasis. Afferent signals such as the hormones insulin and leptin convey information to the brain regarding long-term energy stores, while information regarding short-term energy availability is conveyed by nutrient related signals such as glucose and free fatty acids (FFA). In response to this input, the brain makes adjustments to output systems that control food intake, energy expenditure, hepatic insulin sensitivity, and glucose uptake.”

FIG. 1. Model of CNS regulation of glucose homeostasis. The CNS integrates signals from both long-term energy stores (e.g., leptin) and short-term availability (nutrients; e.g., free fatty acids) and orchestrates responses that coordinate hepatic glucose production, peripheral glucose uptake, and insulin secretion to maintain glucose homeostasis.

“The cloning of the ob gene and the characterization of its gene product, leptin, indicated that body fat content may be under homeostatic control. Available data indicate that leptin is the afferent signal in a negative feedback loop that maintains constancy of adipose tissue mass. Leptin is secreted from adipocytes (bottom left) either as a 16K protein or bound to a soluble form of its receptor (Ob-R). The level of leptin is positively correlated with differences in body fat. Increased leptin results in negative energy balance (energy expenditure > food intake), whereas decreased levels lead to positive energy balance (food intake > energy expenditure). Leptin acts mainly on the hypothalamus (top). Extensive connections exist between the hypothalamus and other brain regions. Leptin acts centrally to decrease food intake and modulate glucose and fat metabolism (right). Peripheral effects on T cells, pancreatic islets and other tissues have also been demonstrated. CVO, circumventricular organ.”

There are at least five different isoforms of the leptin receptor in mouse. All share identical extracellular, ligand-binding domains but they differ at the C terminus. Four of the five have transmembrane domains, but only Ob-Rb encodes all protein motifs capable of activating the Jak–Stat signal transduction pathway. The remaining isoform, Ob-Re, is truncated before the membrane-spanning domain and is secreted. Mutations in Ob-R lead to massive obesity in db mice and fa rats. Most of the mutations affect all of the splice forms. However, in obese C57Bl/Ks db/db mice, the mutation creates a new splice donor that inserts a premature stop codon into the Ob-Rb 3′-end, resulting in the replacement of the Ob-Rb isoform by the Ob-Ra isoform. This mutation establishes the Ob-Rb isoform as being critical for leptin function. WT, wild type.

“Leptin acts as part of a feedback loop to maintain constant stores of fat. A loss of body fat (starvation) leads to a decrease in leptin, which in turn leads to a state of positive energy balance wherein food intake exceeds energy expenditure. A range of other metabolic and endocrine responses is also seen. Conversely, an increase in adiposity leads to an increase in the levels of leptin and a state of negative energy balance, with energy expenditure exceeding food intake. Genetic evidence indicates that different hypothalamic neuropeptides may mediate these responses.

The melanocortin-4 (MC-4) receptor and its ligands, MSH and ART, are probably necessary for the biological response to increasing leptin levels. CRH also mediates some of leptin's effects, as pretreatment with an anti-CRH antibody blunts the anorectic effects of an i.c.v. dose of leptin. Other studies indicate that NPY is an important component of the biological response to low levels of leptin and possibly starvation. Other molecules are likely to play a role in the leptin response. These other factors are largely unknown but probably include some of the molecules shown in Table 1. GnRH, gonadotropin-releasing hormone; GHRH, growth-hormone-releasing hormone.”

There are three general ways in which alterations of the leptin regulatory loop could lead to obesity. 

**a,** Failure to produce leptin, as occurs in ob/ob mice, would result in obesity, as would **b,** inappropriately low leptin secretion for a given fat mass. In the latter case, the fat mass would expand until 'normal' leptin levels are reached, resulting in obesity (also see Fig. 5). **c,** Finally, obesity could result from relative or absolute insensitivity to leptin at its site of action.

Such resistance would be associated with increased circulating leptin, analogous to the increased insulin levels seen with insulin-resistant diabetes. In general, high plasma leptin levels are evident in obese rodents and humans. In a subset of cases, obesity is associated with normal levels of leptin. Differences in leptin production and leptin sensitivity could be the result of genetic, environmental and psychological factors.

“A relative decrease in leptin production by adipose tissue would be expected to lead to obesity. In such a case, the fat cell mass would be predicted to expand until the set point for plasma leptin levels was reached.

Thus obesity with normal leptin levels is inferred to result from a relative decrease in leptin production by adipose tissue.”

Table 1 Hypothalamic modulators of food intake

<table>
<thead>
<tr>
<th>Increase food intake</th>
<th>Decrease food intake</th>
</tr>
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<tbody>
<tr>
<td>NPY</td>
<td>CART</td>
</tr>
<tr>
<td>MCH</td>
<td>CCK</td>
</tr>
<tr>
<td>Galanin</td>
<td>CRH</td>
</tr>
<tr>
<td>Orexin a and b</td>
<td>α-MSH</td>
</tr>
<tr>
<td>Peptide YY</td>
<td>Insulin</td>
</tr>
<tr>
<td>Noradrenaline (α2 receptor)</td>
<td>GLP-1</td>
</tr>
<tr>
<td></td>
<td>Bombesin</td>
</tr>
<tr>
<td></td>
<td>Urocortin</td>
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<td></td>
<td>Serotonin</td>
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</table>

Many factors regulate feeding behaviour. The neurotransmitters and neuropeptides known to regulate food intake are shown. Leptin probably modulates the activity some or all of these factors (and vice versa). A detailed understanding of the functional relationships among leptin and these (and other) neuropeptides and neurotransmitters will be necessary to determine the mechanisms regulating food intake and body weight. GLP-1, glucagon-like peptide-1.
FIG. 2. Leptin receptor signaling. Leptin binding to LepRb mediates activation of the tyrosine kinase Janus kinase-2 (Jak2), resulting in phosphorylation of three tyrosine residues (Tyr985, Tyr1077, Tyr1138). Phosphorylation of Tyr985 recruits SHP-2, leading to the activation of the ERK pathway, and also binds to suppressor of cytokine signaling-3 (SOCS-3), a negative regulator of LepRb signaling. Phosphorylation of Tyr1077 mediates signal transduction and activator of transcription-5 (STAT5). Phosphorylation of Tyr1138 recruits and activates STAT3 and STAT5. Activation of STAT3 leads to increased SOCS-3 expression, which acts as a negative-feedback inhibitor of leptin signaling, in part, by binding to Tyr985 of LepRb. In addition, hypothalamic inflammation is also induced during high-fat feeding and increases SOCS-3 expression. Similar to SOCS-3, protein tyrosine phosphatase (PTP) 1B may also inhibit LepRb signaling via dephosphorylation of Jak2.
Activation of the insulin receptor induces tyrosine phosphorylation of insulin receptor substrate (IRS) proteins, which in turn activate phosphatidylinositol 3-kinase (PI3K), an enzyme that phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3) and activates several downstream molecules including 3-phosphoinositide-dependent protein kinase 1 (PDK1), protein kinase B (PKB; also referred to as Akt), and mammalian target of rapamycin (mTOR).
Leptin binding to the extracellular domain of the LepRb activates Janus kinase-2 (JAK2), leading to binding and tyrosine phosphorylation of STAT3, which dimerizes, translocates to the nucleus, and activates transcription of target genes SOCS-3, which can attenuate both insulin and leptin receptor signaling. Like insulin, leptin signaling can also activate PI3K, and downstream targets, presumably via tyrosine phosphorylation of IRS proteins by Jak2. Although leptin and insulin both have the potential to activate IRS-PI3K signaling in neurons and other cell types, important differences in the response to these two hormones exist. These likely arise from divergent roles for PI3K signaling within a given cell type due to differences in the intracellular microdomain in which PI3K signaling is activated, or from distinct cell subpopulations that respond to either leptin or insulin, but not both (e.g., POMC neurons). PTEN, phosphatase and tensin homolog.
The hypothalamic ARC contains neuropeptide Y and agouti-related peptide (NPY/AgRP) neurons that stimulate food intake and are inhibited by leptin, and proopiomelanocortin (POMC) neurons that reduce food intake and are stimulated by leptin.

NPY/AgRP neurons also inhibit POMC neurons via synaptic release of the neurotransmitter GABA. ARC, arcuate nucleus; LepRb, leptin receptor; Mc3r/Mc4r, melanocortin-3/4 receptor.

Model of the hypothalamic regulation of hepatic glucose production.

Leptin-sensing neurons in the hypothalamic ARC receive input regarding energy stores, and in response to this input, pathways that increase hepatic vagal tone to the liver are activated, increasing hepatic insulin sensitivity.

ARC, arcuate nucleus; LepRb, leptin receptor; NTS, nucleus of the solitary tract; G6Pase, glucose-6-phosphatase; PEPCK, phosphoenolpyruvate kinase.
Rapid Rewiring of Arcuate Nucleus Feeding Circuits by Leptin

Shirly Pinto,1* Aaron G. Roseberry,1* Hongyan Liu,1*
Sabrina Diano,3 Marya Shanabrough,3 Xiaoli Cai,1,2
Jeffrey M. Friedman,1,2† Tamas L. Horvath3,4†

The fat-derived hormone leptin regulates energy balance in part by modulating the activity of neuropeptide Y and proopiomelanocortin neurons in the hypothalamic arcuate nucleus. To study the intrinsic activity of these neurons and their responses to leptin, we generated mice that express distinct green fluorescent proteins in these two neuronal types. Leptin-deficient (ob/ob) mice differed from wild-type mice in the numbers of excitatory and inhibitory synapses and postsynaptic currents onto neuropeptide Y and proopiomelanocortin neurons. When leptin was delivered systemically to ob/ob mice, the synaptic density rapidly normalized, an effect detectable within 6 hours, several hours before leptin’s effect on food intake. These data suggest that leptin-mediated plasticity in the ob/ob hypothalamus may underlie some of the hormone’s behavioral effects.
Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency

I. Sadaf Farooqi,1 Giuseppe Matarese,2 Graham M. Lord,3 Julia M. Keogh,1 Elizabeth Lawrence,4 Chizzo Agwu,5 Veronica Sanna,2 Susan A. Jebb,5 Francesco Perna,7 Silvia Fontana,2 Robert I. Lechler,5 Alex M. DePaoli,3 and Stephen O’Rahilly3

1University Department of Medicine and Department of Clinical Biochemistry, Addenbrooke’s Hospital, Cambridge, United Kingdom
2Centro di Endocrinologia ed Oncologia Sperimentale, Consiglio Nazionale delle Ricerche (CNR-CEROS), Naples, Italy
3Department of Immunology, Imperial College School of Medicine, Hammersmith Hospital, London, United Kingdom
4AMGEN Inc., Thousand Oaks, California, USA
5Department of Paediatrics, Sandwell Hospital, West Midlands, United Kingdom
6Medical Research Council, Human Nutrition Research, Cambridge, United Kingdom
7Cattedra di Malattie dell’Apparato Respiratorio, Dipartimento di Medicina Clinica e Sperimentale, Università di Napoli Federico II, Naples, Italy

The wide range of phenotypic abnormalities seen in the leptin-deficient ob/ob mouse and their reversibility by leptin administration provide compelling evidence for the existence of multiple physiological functions of this hormone in rodents. In contrast, information regarding the roles of this hormone in humans is limited. Three morbidly obese children, who were congenitally deficient in leptin, were treated with daily subcutaneous injections of recombinant human leptin for up to 4 years with sustained, beneficial effects on appetite, fat mass, hyperinsulinemia, and hyperlipidemia. Leptin therapy resulted in a rapid and sustained increase in plasma thyroid hormone levels and, through its age-dependent effects on gonadotropin secretion, facilitated appropriately timed pubertal development. Leptin deficiency was associated with reduced numbers of circulating CD4+ T cells and impaired T cell proliferation and cytokine release, all of which were reversed by recombinant human leptin administration. The subcutaneous administration of recombinant human leptin has major and sustained beneficial effects on the multiple phenotypic abnormalities associated with congenital human leptin deficiency.

CLINICAL CASE SEMINAR

Congenital Leptin Deficiency Due to Homozygosity for the Δ133G Mutation: Report of Another Case and Evaluation of Response to Four Years of Leptin Therapy

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University Department of Clinical Biochemistry, Cambridge Institute for Medical Research, Addenbrooke’s Hospital (W.T.G., I.S.F., S.O.), Cambridge, United Kingdom CB2 2XY; Department of Pediatric Endocrinology, Alberta Children’s Hospital (M.M., R.A.T.), Calgary, Alberta, Canada T2T 5C7; and Amgen, Inc. (A.M.D., E.L.), Thousand Oaks, California 91320-1799

Congenital leptin deficiency is a rare, but treatable, cause of severe early-onset obesity. To date, two United Kingdom families of Pakistani origin carrying a frameshift/premature stop mutation, c.398delG (Δ133G), and one Turkish family carrying a missense mutation, c.313C>T (Arg105Trp), have been described. Affected subjects are homozygotes and manifest severe obesity and hyperphagia accompanied by metabolic, neuroendocrine, and immune dysfunction. The effects of recombinant leptin therapy have been reported in three children with the Δ133G mutation, and in all cases this has led to a dramatic resolution of clinical and biochemical abnormalities. We now report a Canadian child, of Pakistani origin but unrelated to the previously reported subjects, presenting with severe hyperphagia and obesity, who was found to be homozygous for the Δ133G mutation. In this child, 4 yr of therapy with sc injections of recombinant leptin provided additional evidence for the sustained beneficial effects of leptin replacement on fat mass, hyperinsulinemia, and hyperlipidemia. In addition, leptin administration corrected abnormal thyroid biochemistry and allowed the withdrawal of T4 treatment, providing additional support for the role of leptin in the regulation of the human hypothalamic-pituitary-thyroid axis. (J Clin Endocrinol Metab 89: 4821–4826, 2004)
Obesity Management

Ten years of leptin replacement therapy

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Received 30 August 2010; revised 19 October 2010; accepted 21 October 2010

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Summary

Leptin is a pleiotropic cytokine-like hormone that is involved in the regulation of energy intake and expenditure, neuroendocrine function, immunity and lipid and glucose metabolism. The few humans with genetically based leptin deficiency provide a unique model to assess these effects. We have identified five Turkish patients (one male and two female adults; one boy and one girl) with congenital leptin deficiency due to a missense mutation in the leptin gene. Four of these patients were treated with physiological doses of recombinant methionyl human leptin. Body composition, brain structure and function, behaviour, immunity and endocrine and metabolic parameters were evaluated before and during treatment. Our results showed that leptin has peripheral, hypothalamic and extra-hypothalamic effects. Within the endocrine system, leptin regulates the circadian rhythms of cortisol, thyroid-stimulating hormone, luteinizing hormone and follicle-stimulating hormone. In the brain, leptin controls energy balance and body weight, and plays a role on neurogenesis and brain function. Leptin is a key element of the adipose tissue axis, enhances immune response, and regulates inflammation, coagulation, fibronolysis and platelet aggregation. Our 10-year experience in treating these unique patients provided valuable data on the peripheral and central effects of leptin. Those results can be taken into account for the development of leptin-based therapies for other diseases.

Keywords: Leptin, obesity, recombinant methionyl human leptin.

*obesity* reviews (2011) 12, e315–e323
With Liposuction, the Belly Finds What the Thighs Lose

By GINA KOLATA
Published: April 30, 2011
**Figure 2**

Effects of r-metHuLeptin therapy on energy intake. (a) Energy intake at an ad libitum test meal before (black bars) and 2 months after (white bars) r-metHuLeptin therapy in child A, B, and C. Energy intake (KJ) expressed per kilogram lean body mass to compare intake of subjects of different age and body size. (b) Changes in body mass index SDS (BMI SDS) (filled symbols) and energy intake at an 18-MJ ad libitum test meal (gray bars) during 36 months of treatment in child B. Panels indicate duration of r-metHuLeptin dose expressed as a percentage of predicted serum leptin concentration based on age, gender, and body composition.

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<td>Immunity</td>
<td>Decrease in triglycerides and increase in high-density lipoprotein cholesterol (HDL-C)</td>
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<td>Inhibition of lipogenesis and stimulation of lipolysis</td>
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<td>Leptin withdrawal: changes towards a decreased state of thermogenesis and increased fat breakdown</td>
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<td>Decrease in the absolute lymphocyte count (CD3, CD4, CD19 cells)*</td>
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<td>Increased T-cell responsiveness*</td>
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* Alterations assessed exclusively in patient D. 

Our results are important not only to guide the treatment of leptin-deficient patients — including those with lipodystrophy syndromes, but also to direct future studies on the usefulness of leptin in treating or preventing other diseases or conditions, such as common obesity, lipodystrophy syndromes, diabetes, hypothalamic amenorrhea, anorexia nervosa, mood and cognitive disorders, immune deficiencies and lipodystrophy.
Clinical Spectrum of Obesity and Mutations in the Melanocortin 4 Receptor Gene

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BACKGROUND
Melanocortin 4 receptor (MC4R) deficiency is the commonest monogenic form of obesity. However, the clinical spectrum and mode of inheritance have not been defined, pathophysiological mechanisms leading to obesity are poorly understood, and there is little information regarding genotype–phenotype correlations.

METHODS
We determined the nucleotide sequence of the MC4R gene in 500 probands with severe childhood obesity. Family studies were undertaken to examine cosegregation of identified mutations with obesity. Subjects with MC4R deficiency underwent metabolic and endocrine evaluation; the results were correlated with the signaling properties of mutant receptors.
RESULTS
Twenty-nine probands (5.8 percent) had mutations in MC4R; 23 were heterozygous, and 6 were homozygous. Mutation carriers had severe obesity, increased lean mass, increased linear growth, hyperphagia, and severe hyperinsulinemia; homozygotes were more severely affected than heterozygotes. Subjects with mutations retaining residual signaling capacity had a less severe phenotype.

CONCLUSIONS
Mutations in MC4R result in a distinct obesity syndrome that is inherited in a codominant manner. Mutations leading to complete loss of function are associated with a more severe phenotype. The correlation between the signaling properties of these mutant receptors and energy intake emphasizes the key role of this receptor in the control of eating behavior in humans.
Aldosterone, the main mineralocorticoid hormone, is a steroid hormone produced by the zona glomerulosa of the adrenal cortex in the adrenal gland.\(^1\)\(^2\) It is essential for sodium conservation in the kidney, salivary glands, sweat glands and colon.\(^3\) It plays a central role in the regulation of the plasma sodium (Na\(^+\)), the extracellular potassium (K\(^+\)) and arterial blood pressure. It does so mainly by acting on the mineralocorticoid receptors in the distal tubules and collecting ducts of the nephron.\(^3\) It influences the reabsorption of sodium and excretion of potassium (from and into the tubular fluids, respectively) of the kidney, thereby indirectly influencing water retention or loss, blood pressure and blood volume.\(^4\) When dysregulated, aldosterone is pathogenic and contributes to the development and progression of cardiovascular and renal disease.\(^5\) Aldosterone has exactly the opposite function of the atrial natriuretic hormone secreted by the heart.\(^4\)

Aldosterone is part of the renin–angiotensin system. It has a plasma half-life of under 20 minutes.\(^6\) Drugs that interfere with the secretion or action of aldosterone are in use as antihypertensives, like lisinopril, which lowers blood pressure by blocking the angiotensin-converting enzyme (ACE), leading to lower aldosterone secretion. The net effect of these drugs is to reduce sodium and water retention but increase retention of potassium. Another example is spironolactone, a potassium-sparing diuretic of the steroidal spirolactone group, which decreases blood pressure by releasing fluid from the body while retaining potassium.

Aldosterone was first isolated by Simpson and Tait in 1953.\(^7\)
Cardiovascular Disease & Leptin

Leptin $\rightarrow$ ↑ activity of cardiovascular system

Leptin $\rightarrow$ ↑ Aldosterone synthase (adrenal glands)

$\Rightarrow$ ↑ Aldosterone $\Rightarrow$ ↑ inflammation, blood vessel stiffness, impaired insulin sensitivity

$\uparrow$ blood pressure and salt-water regulation