Leptin and the Central Nervous System Control of Glucose Metabolism

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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 Sекretes hormones that regulate

1. APPETITE
2. METABOLISM
The role of depot fat in the hypothalamic control of food intake in the rat

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The young rat adjusts its food intake so precisely to its energy needs that its fat stores remain almost constant. Considerable variation in food intake is brought about in response to change in heat loss to the environment, or in loss of food through the mammary gland in lactation, without appreciable change of weight. Hypothalamic damage permits excessive intake and causes obesity. The degree of obesity and in general its rate of development, is a function of the degree of damage to the region of the tuber cinereum, and is independent of changes of intake with environmental temperature. It is suggested that the hypothalamic satiety mechanism is concerned only in the prevention of an overall surplus of energy intake over expenditure, which would cause the deposition of fat in the depots. The simplest way in which this lipostasis could be achieved is by sensitivity to the concentration of circulating metabolites. There is no disturbance of temperature regulation or acclimatization to changed environmental temperature in obese rats. These findings do not support the suggestion made by Brobeck (1946) that food intake is controlled as part of the normal regulation of body temperature by a thermostensitive hypothalamic centre.

The maximum daily intake of food during hyperphagia appears to be determined by some limiting factor additional to the hypothalamic mechanism. A similar factor appears to operate in lactation. Reasons are advanced for regarding this as the limiting rate at which absorbed foodstuffs can be removed from the circulation, that is as some aspect of the synthesis or transport of fat.
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
Information about long-term energy stores leads to leptin, which affects hunger and satiety.

Energy stores & nutrient availability:
- Long-term:
  - Leptin
  - All about food consumed relative to energy
  - Expended
- Short-term:
  - Glucose
  - FFA
  - Body temperature
  - Plasma amino acids
  - CCK

Food intake meter:
- Hunger
- Satiety

Eating food increases energy expenditure.

Peripheral glucose uptake.

Insulin sensitivity:
- Endogenous glucose production.
Leptin & Insulin

INFO ABOUT LONG-TERM ENERGY STORES

INFO ABOUT SHORT-TERM ENERGY AVAILABILITY

GLUCOSE & FREE FATTY ACIDS
Reduced energy stores?

If NO:
- Nutrient abundance & excess energy storage

If YES:
- Need to promote positive energy balance
Reduced energy stores

Nutrient abundance & excess energy storage

NO

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

Need to promote positive energy balance

1. Increase food intake
2. Reduce energy expenditure
3. Increase nutrient availability and endogenous glucose production
4. Fat metabolism
Availability of Energy Stores

**ENERGY BALANCE**

- **positive energy balance**
- **negative energy balance**

- **food intake**
- **energy expenditure**
- **endogenous glucose production**

- **eat**
- **energy**
- **glucose**

**Availability of Energy Stores**
**LEPTIN FACTS**

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

   - Leptin
   - Adipose mass
   - Leptin mass in plasma

2. **Behavioral changes**
   - Leptin → negative energy balance
     - Energy expenditure > food intake

3. **Positive energy balance**
   - Leptin in plasma
   - Peripheral effects
     - β cells
     - T cells
   - Decreased plasma levels of leptin signal nutrient deprivation
2. INJECTION OF LEPTIN INTO PLASMA:
   - REDUCTION OF BODY WEIGHT (CLOSER DEPENDENT !!)
   - ↓ ADIPOCYTES MASS DECREASED
   - NO CHANGE IN LEAN MUSCLE MASS
   - ↑ LEPTIN INJ \( \Rightarrow \) ↓ WEIGHT
   - INJECTION & PHYSIOLOGICAL LEVELS
③ Leptin levels: "long-term" signal
- Do not change significantly after meals
- Does not cause meal termination (by itself)
4. NO LEPTIN

06/06 mice exhibit the same effects seen in starved animals.

- db/db mice lack leptin receptor & have same phenotype as 06/06

Perceived starvation:

- Decreased body temperatures
- Increased food consumption (hyperphagia)
- Decreased energy expenditure (less activity)
- Decreased immune function
- Infertility

Leptin regulates onset of puberty & estrous cycle.

Leptin links nutritional state & the immune system.

Leptin stimulates proliferation of CD4+ T cells & production of cytokines by Th helper-1 cells.

Leptin is replaced in 06/06 mice, these abnormalities go away.
Leptin acts centrally by:

- Inhibit appetite

- Decreasing activity of orexigenic neurons
  - NPY
  - AgRP
  - GABA

- Increasing activity in anorexigenic neurons
  - POMC
  - CART

Key:
- Orexigenic: eat
- Anorexigenic: eat

Diagram showing various brain nuclei and connections, including R leptin receptor (LEPRβ).
RESPONSE TO STARVATION

ACTIVATE NPY ORXIGENIC PATHWAYS

↑ FOOD INTAKE  ↓ ENERGY EXPENDITURE  ↓ SYMPATHETIC TONE

LOOSE WEIGHT

↑ LEPTIN

GAIN WEIGHT

RESPONSE TO OBESITY

ACTIVATE ANOREXIGENIC PATHWAYS

↑ FOOD INTAKE  ↑ ENERGY EXPENDITURE  ↑ SYMPATHETIC TONE

NEGATIVE ENERGY STATE  NEGATIVE ENERGY EXPENDITURE  FOOD INTAKE
Leptin Dysregulation

1. No leptin produced $\Rightarrow$ Obesity

   $\text{ob/ob} \rightarrow \text{no leptin}$

   $\Rightarrow$ Constant starvation signal

   $\Rightarrow$ Promote positive energy balance

   $\downarrow$ Food intake

   $\downarrow$ Energy expenditure

   $\downarrow$ Nutrient availability (fat/glucose)
LOW LEPTIN SECRETION FOR A GIVEN FAT MASS

Actual Fat Mass

This leads to signals that will increase fat mass so the result would be obesity.
LEPTIN INSensitivity

1. db/db phenotype
   a. absolute insensitivity
   b. no matter the [leptin] plasma
      the signals are rated
      that there is not
      enough leptin
   c. result is to promote
      POSITIVE ENERGY BALANCE
      i. food intake 
         energy 
         expenditure 
         nutrient 
         output (fat/glucose)
   d. obesity

2. Leptin Receptor insensitivity/resistance
   a. similar to db/db but
      not as severe.
   b. high levels of leptin in
      plasma
Leptin deficiency

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Endocrine effects</td>
<td>Reversal of type 2 diabetes</td>
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<tr>
<td></td>
<td>Increase in insulin sensitivity, decrease in insulin secretion and in hepatic extraction</td>
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<tr>
<td></td>
<td>Reversal of hypogonadal hypogonadism</td>
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<td>Increase in 24-h cisternisemia, with changes in rhythmicity towards a more regular pattern</td>
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<td>Increase in insulin-like growth factor binding protein (IGFBP1) and insulin-like growth factor binding protein (IGFBP2)</td>
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<td>Maintenance of adequate growth velocity</td>
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<td></td>
<td>Regulation of the thyroid-stimulating hormone (TSH) rhythmicity</td>
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<td>Body composition</td>
<td>Weight loss, mostly fat – up to 54% of initial body weight</td>
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<td>Brain and behaviour</td>
<td>Decrease in caloric intake, with changes in food preference</td>
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<td>Increase in physical activity</td>
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<td>Increase in grey matter concentration</td>
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<td>Activation of brain areas involved with satiety and inhibition of areas involved with hunger</td>
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<td></td>
<td>Increase in cognitive development</td>
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<td></td>
<td>Changes from docile and infantile to assertive and adult-like behaviour</td>
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<tr>
<td>Metabolic effects</td>
<td>Lower decrease in energy expenditure after weight loss</td>
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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, fibrinolysis and platelet aggregation</td>
<td>Leptin withdrawal: changes towards a decreased state of thrombogenesis and increased fibrinolysis</td>
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<tr>
<td>Immunity</td>
<td>Decrease in the absolute lymphocyte count (CD3, CD4, CD19 cells)</td>
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<td></td>
<td>Increased T-cell responsiveness</td>
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* Alterations assessed exclusively in patient D.
Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency

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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 puberal 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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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 (Arg104Trp), 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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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 those 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 adiposinsular axis, enhances immune response, and regulates inflammation, coagulation, fibrinolysis 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.

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With Liposuction, the Belly Finds What the Thighs Lose

By GINA KOLATA
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