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Leptin and the Central Nervous System Control of Glucose Metabolism

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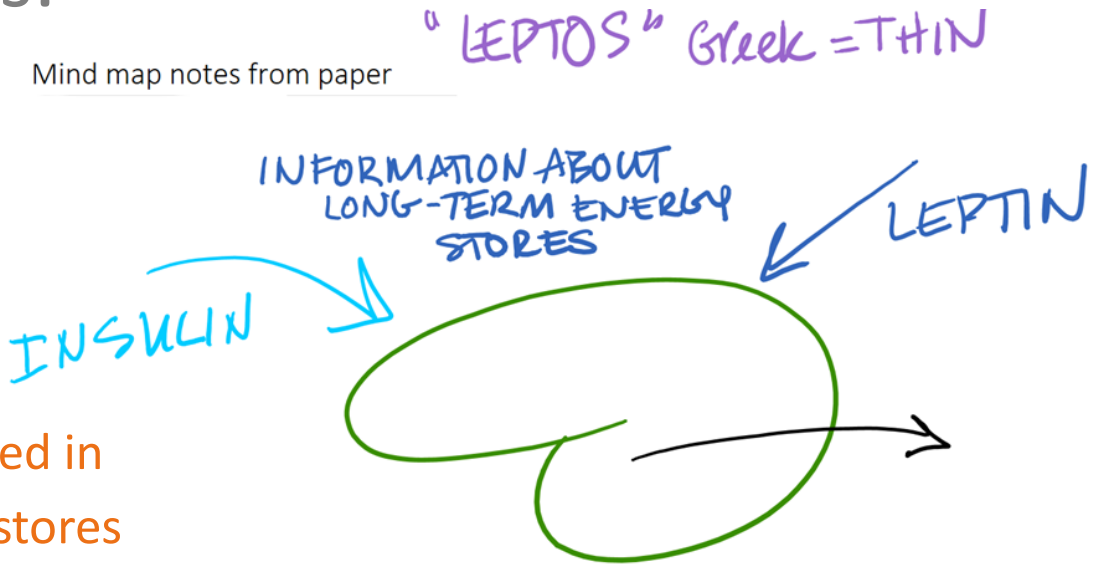
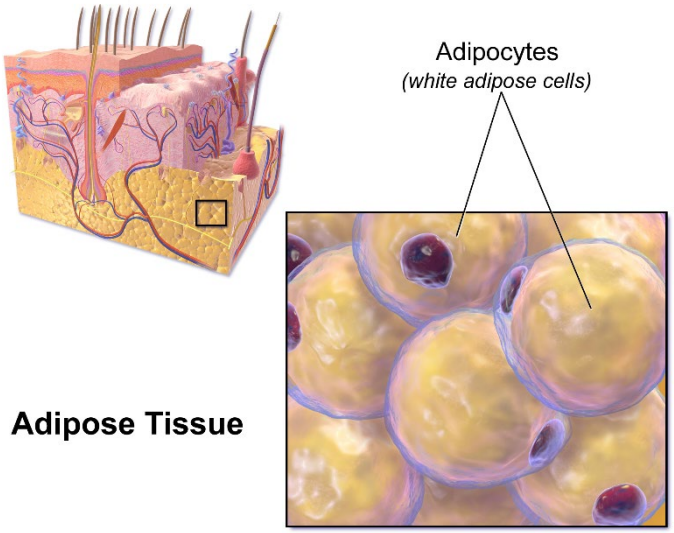
Mind Map Notes:

Mind map notes from paper



Hormonal signals produced in proportion to body fat stores *act centrally* to form a **negative feedback** loop to maintain **HOMEOSTASIS.**



Adipose Tissue

NOTE: ADIPOSE TISSUE

↑ IS AN ENDOCRINE ORGAN

→ communicates w/ BRAIN & PERIPHERY

secretes hormones that regulate

① APPETITE

② METABOLISM

Image: wikimedia.org

The role of depot fat in the hypothalamic control of food intake in the rat

By G. C. Kennedy
National Institute for Medical Research, London, N.W. 7

(*Communicated by A. S. Parkes, F.R.S.—Received* 21 *March* 1952—
Revised 31 *July* 1952)

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 thermosensitive 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.

Kennedy GC. The Role of Depot Fat in the Hypothalamic Control of Food Intake in the Rat. Proc R Soc B Biol Sci [Internet]. 1953;140:578–92. Available from:
http://www.ncbi.nlm.nih.gov/pubmed/13027283\nhttp://rspb.royalsocietypublishing.org/cgi/doi/10.1098/rspb.1953.0009

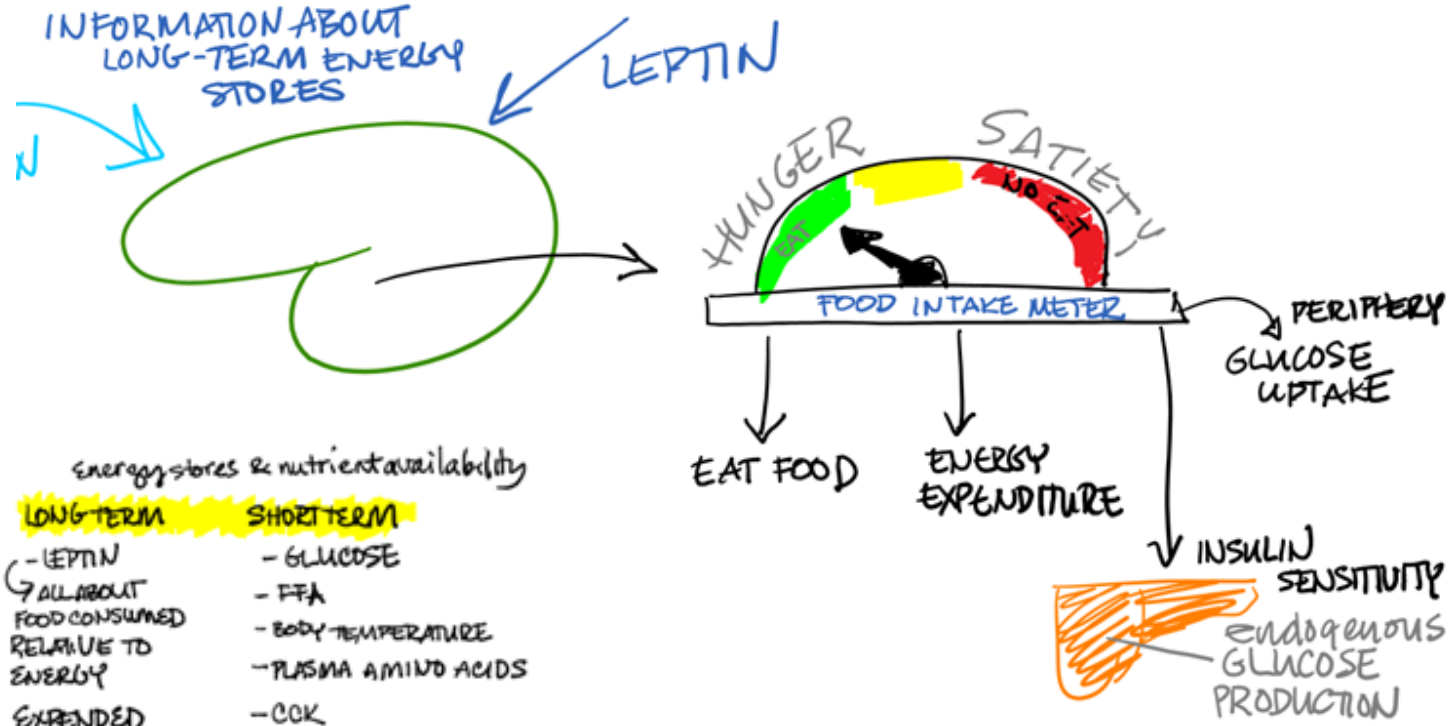
LEPTIN FUNCTIONALITY IS DEPENDENT ON (4) FACTORS

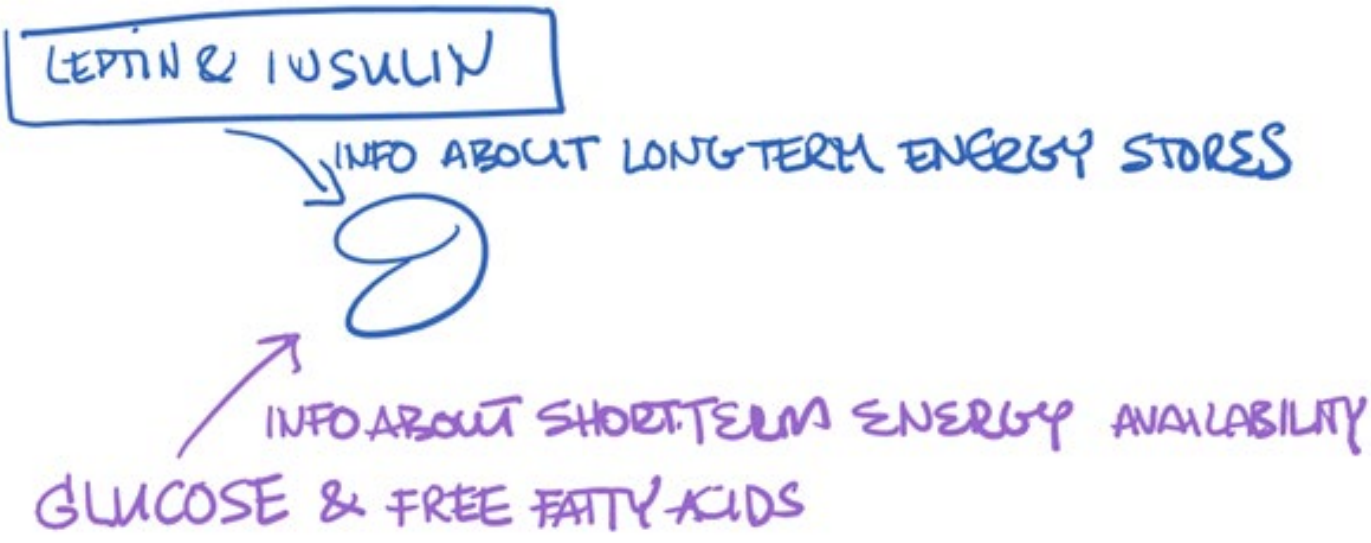
(A) LOCATION
visceral vs subcutaneous

(B) SIZE
large vs small

(C) ADIPOCYTE METABOLISM OF GLUCOSE

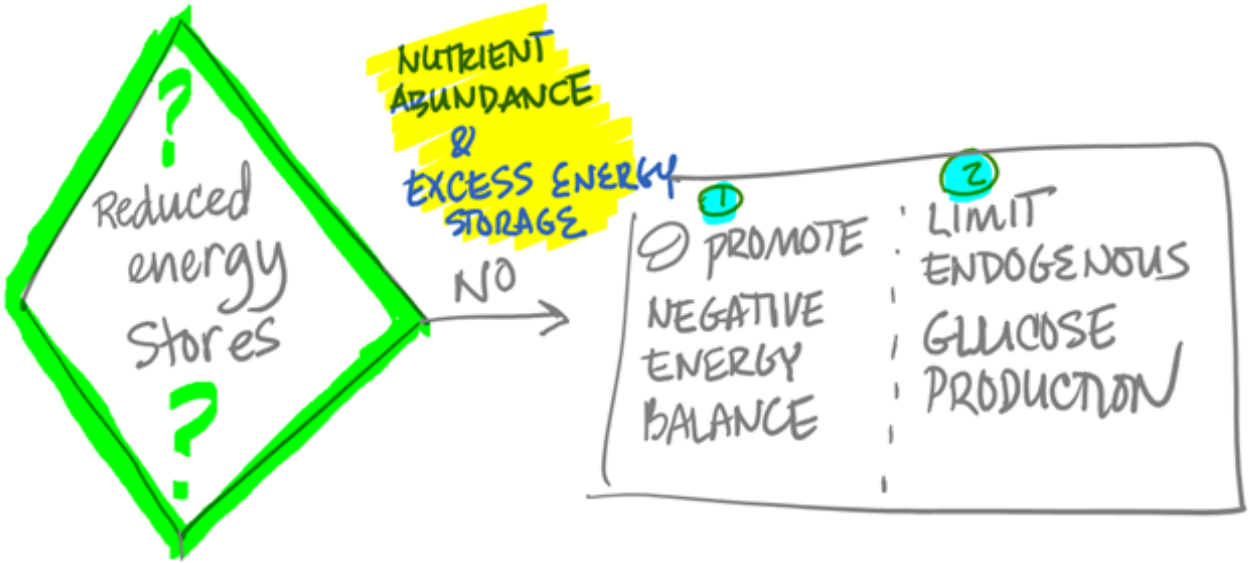
(D) CORTICO-STEROIDS

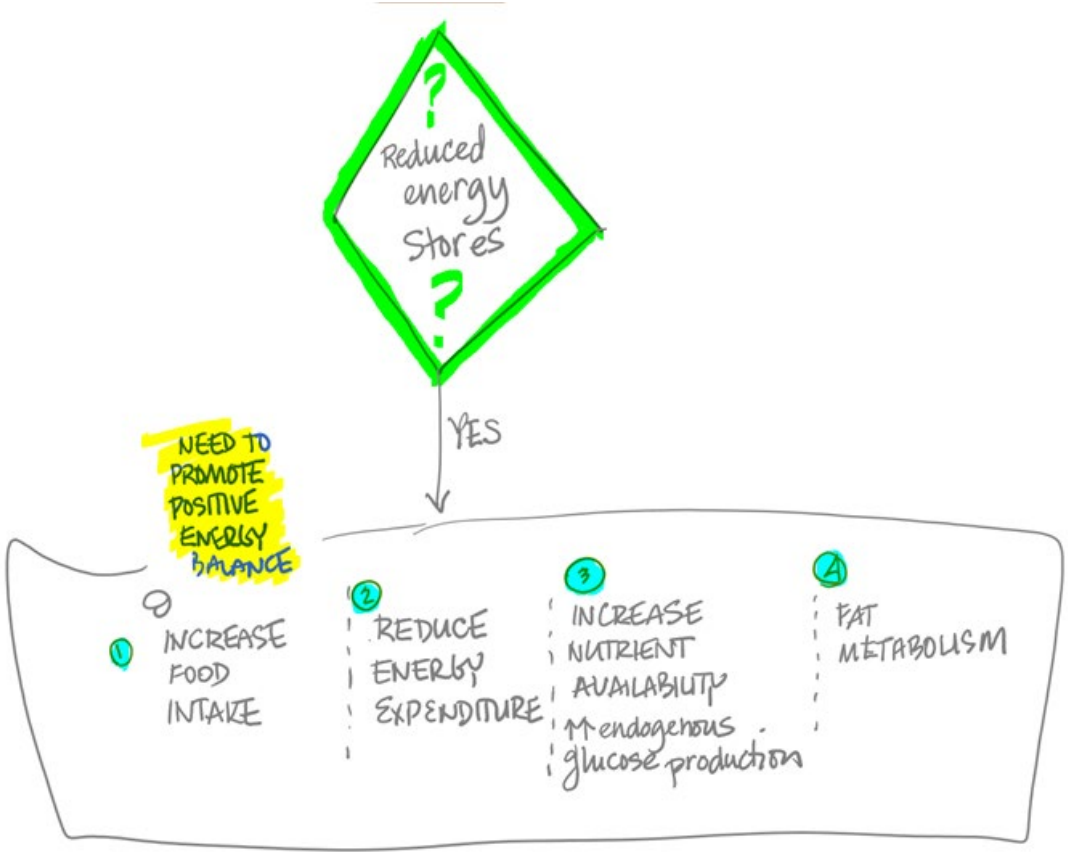

INFORMATION ABOUT LONG-TERM ENERGY STORES
LEPTIN
HUNGER
SATIETY
EAT
DO NOT EAT
FOOD INTAKE METER
PERIPHERY
GLUCOSE UPTAKE
EAT FOOD
ENERGY EXPENDITURE
INSULIN SENSITIVITY
endogenous GLUCOSE PRODUCTION
energy stores & nutrient availability
LONG-TERM
- LEPTIN
↳ ALL ABOUT FOOD CONSUMED RELATIVE TO ENERGY EXPENDED
SHORT TERM
- GLUCOSE
- FFA
- BODY TEMPERATURE
- PLASMA AMINO ACIDS
- CCK


LEPTIN & INSULIN
INFO ABOUT LONGTERM ENERGY STORES
INFO ABOUT SHORTTERM ENERGY AVAILABILITY
GLUCOSE & FREE FATTY ACIDS

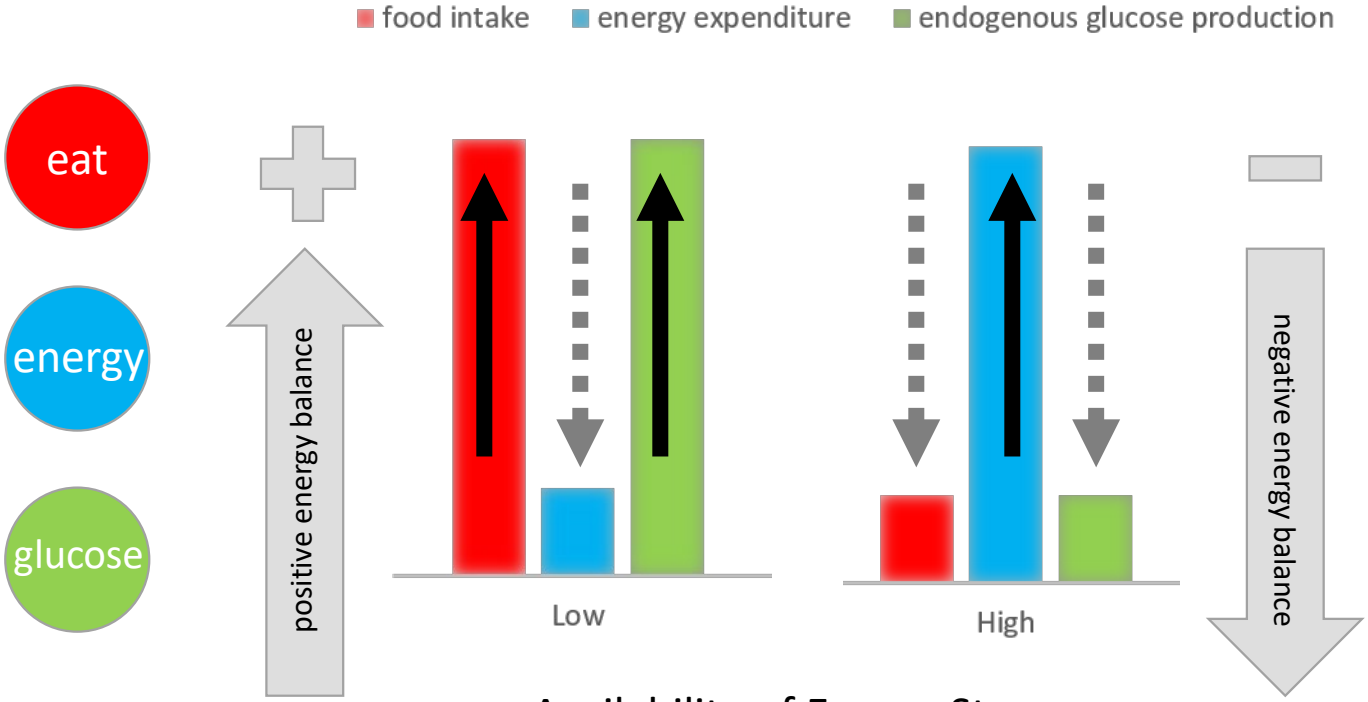
NUTRIENT ABUNDANCE & EXCESS ENERGY STORAGE

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
?
YES
NEED TO PROMOTE POSITIVE ENERGY BALANCE
1
INCREASE FOOD INTAKE
2
REDUCE ENERGY EXPENDITURE
3
INCREASE NUTRIENT AVAILABILITY
↑ endogenous glucose production
4
FAT METABOLISM

ENERGY BALANCE

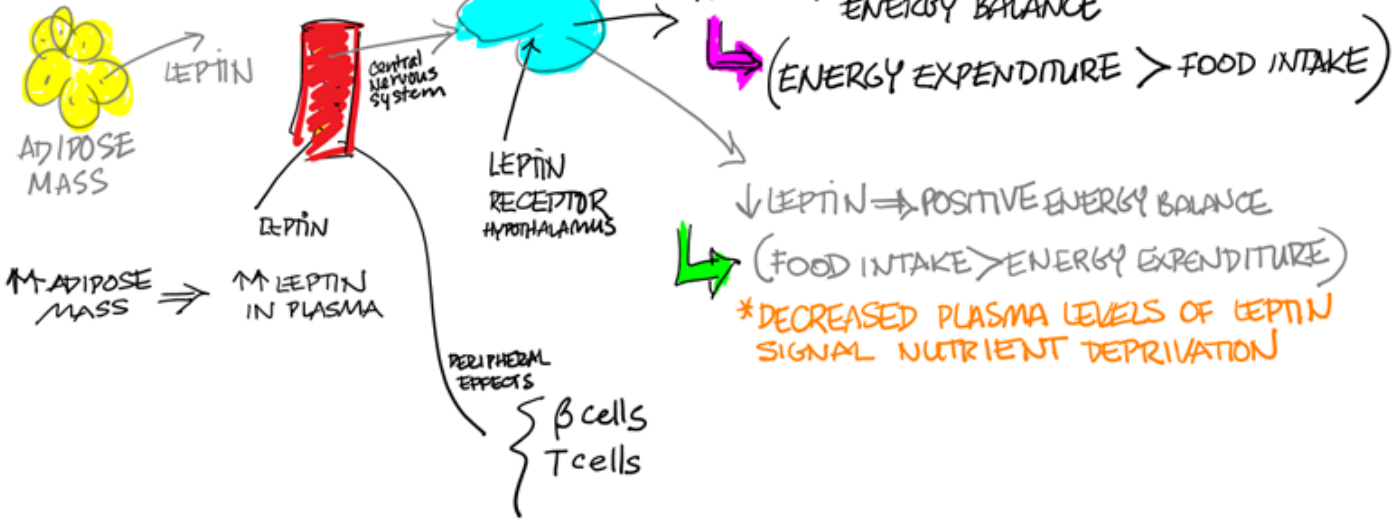


Availability of Energy Stores

LEPTIN FACTS

* EXPRESSED IN ADIPOSE TISSUES
  GASTRIC EPITHELIUM
  PLACENTA
  ↑ HIGHEST LEVELS

1. PLASMA LEVELS OF LEPTIN ARE COORELLATED WITH ADIPOSE TISSUE MASS



~ BEHAVIORAL CHANGES ~

↑LEPTIN ⇒ NEGATIVE ENERGY BALANCE

(ENERGY EXPENDITURE > FOOD INTAKE)

↓LEPTIN ⇒ POSITIVE ENERGY BALANCE

(FOOD INTAKE > ENERGY EXPENDITURE)

* DECREASED PLASMA LEVELS OF LEPTIN SIGNAL NUTRIENT DEPRIVATION

(2) INJECTION OF LEPTIN INTO PLASMA:

injection @ physiological levels

↳ REDUCTION OF BODY WEIGHT (dose dependent !!)

↓ADIPOCYTES MASS DECREASED

NO CHANGE IN LEAN MUSCLE MASS

↑LEPTIN INJ ⇒ ↓WEIGHT

(3) LEPTIN LEVELS ← "LONGTERM" SIGNAL

- DO NOT CHANGE SIGNIFICANTLY AFTER MEALS
- DOES NOT CAUSE MEAL TERMINATION (BY ITSELF)

(4) ob/ob (NO LEPTIN) MICE EXHIBIT THE SAME EFFECTS SEEN IN STARVED ANIMALS –

db/db MICE LACK LEPTIN RECEPTOR & HAVE SAME PHENOTYPE AS ob/ob

"PERCEIVED STARVATION"

eg)

- ↓ DECREASED BODY TEMPERATURES
- ↑ FOOD CONSUMPTION (HYPERPHASIA) → LEADS TO OBESITY IN THE PRESENCE OF FOOD
- ↓ DECREASED ENERGY EXPENDITURE (↓ ACTIVITY)
- ↓ DECREASED IMMUNE FUNCTION ← LEPTIN STIMULATES PROLIFERATION OF $CD4^+$ T CELLS, ↑ PRODUCTION OF CYTOKINES BY T-helper-1 CELLS } LEPTIN LINKS NUTRITIONAL STATE & THE IMMUNE SYSTEM
- INFERTILITY ← THYROID & CORTICOSTERONE HORMONES ARE AFFECTED BY LEPTIN LEVELS
  - LEPTIN REGULATES ONSET OF PUBERTY (♀ ESTROUS CYCLE)

WHEN LEPTIN IS REPLACED IN ob/ob MICE THESE ABNORMALITIES GO AWAY.

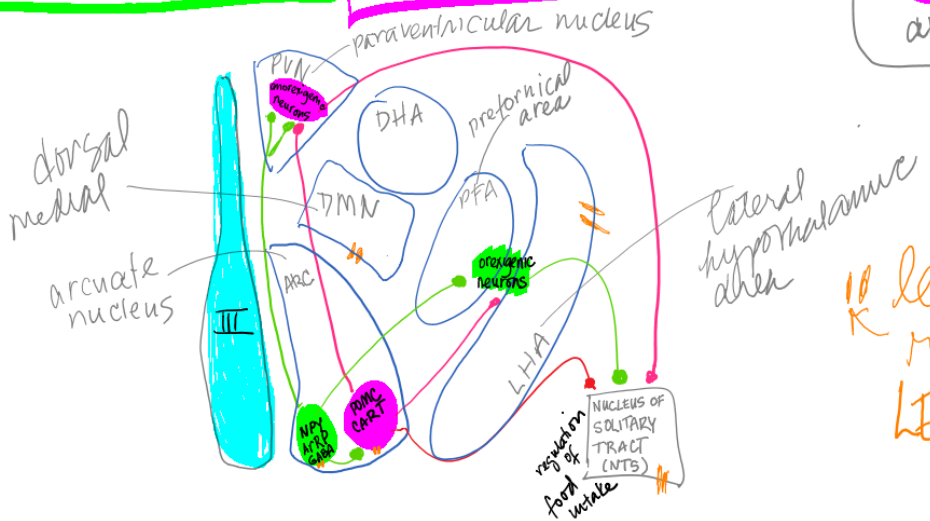
(5) LEPTIN ACTS CENTRALLY BY:

INHIBIT APPETITE

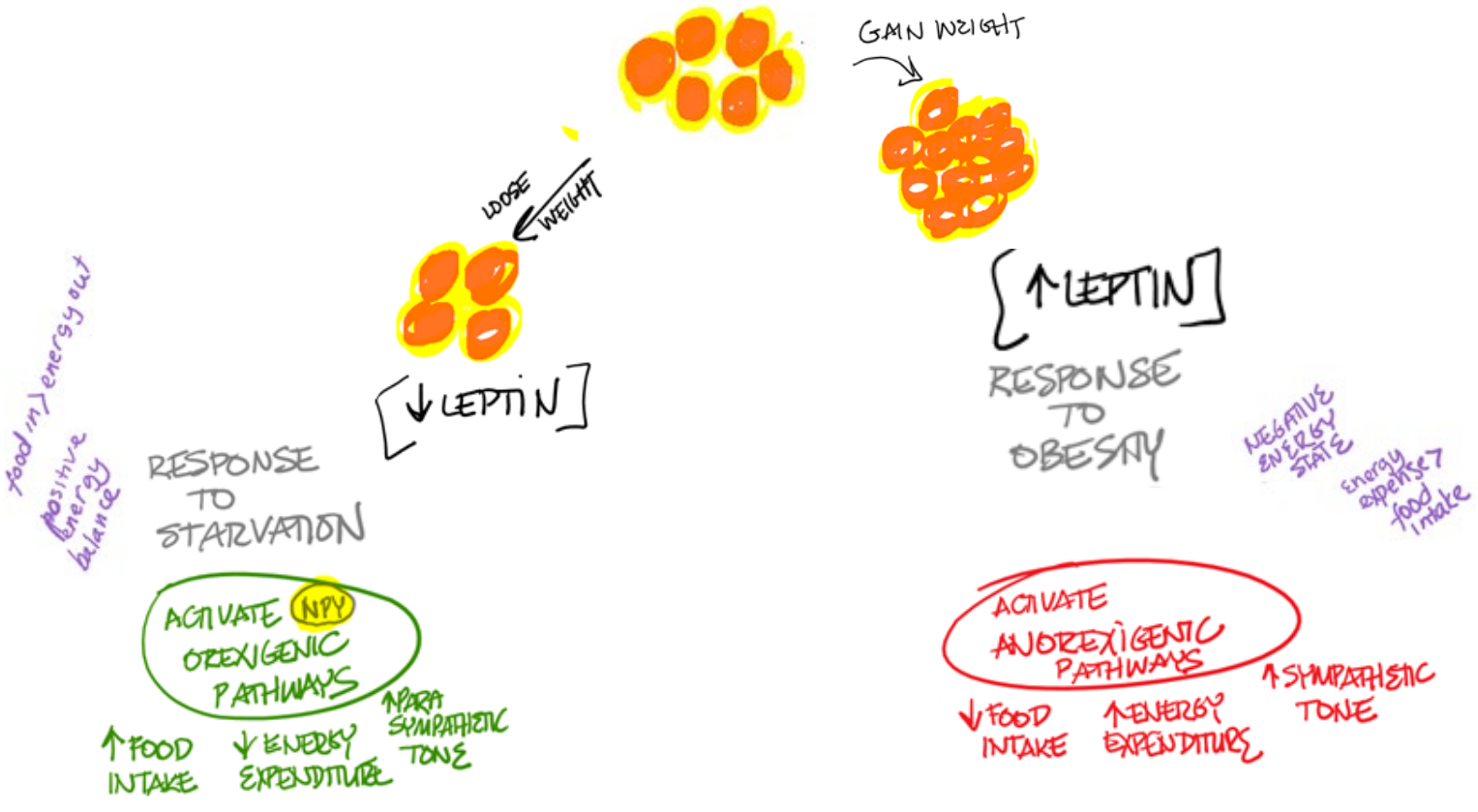
↓ decreasing activity of orexigenic neurons
- NPY
- AgRP
- GABA

↑ INCREASING ACTIVITY IN ANOREXIGENIC NEURONS
- POMC
- CART

Key
- orexigenic
  - ← eat
- ← no eat
  - anorexigenic



leptin receptor LEPRb


GAIN WEIGHT
LOOSE WEIGHT
[↓LEPTIN]
[↑LEPTIN]
RESPONSE TO STARVATION
RESPONSE TO OBESITY
food in / energy out
positive energy balance
NEGATIVE ENERGY STATE
energy expense ? food intake
ACTIVATE NPY OREXIGENIC PATHWAYS
↑FOOD INTAKE
↓ENERGY EXPENDITURE
↑PARA SYMPATHETIC TONE
ACTIVATE ANOREXIGENIC PATHWAYS
↓FOOD INTAKE
↑ENERGY EXPENDITURE
↑SYMPATHETIC TONE

LEPTIN DYSREGULATION

1. NO LEPTIN PRODUCED ⇒ OBESITY

ob/ob → no leptin

↳ CONSTANT STARVATION SIGNAL

↳ PROMOTE POSITIVE ENERGY BALANCE

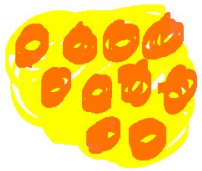
- ↑↑ FOOD INTAKE
- ↓↓ ENERGY EXPENDITURE
- ↑↑ NUTRIENT AVAILABILITY (FAT/GLUCOSE)

2 LOW LEPTIN SECRETION FOR A GIVEN FAT MASS

ACTUAL FAT MASS

the amount of leptin produced is equivalent to

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

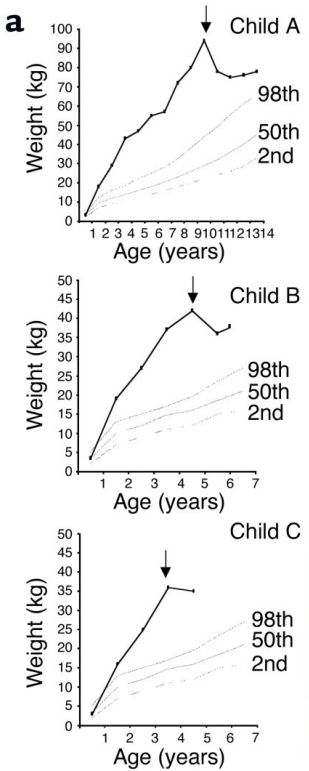


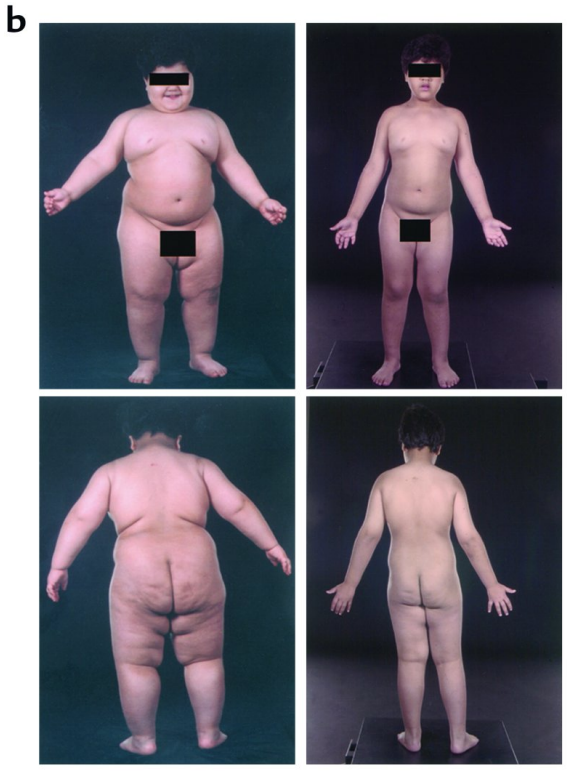
obesity.

(3) LEPTIN INSENSITIVITY

(a) db/db phenotype
↳ absolute insensitivity
↳ no matter the $[leptin]_{plasma}$
the signals are xmted
that there is not
enough leptin
↳ result is to promote
POSITIVE ENERGY BALANCE
↓
↑↑ food intake ↓↓ energy expenditure ↑↑ nutrient avail. (FAT/GLUCOSE)
⇒ obesity

(b) Leptin Receptor insensitivity/resistance
↳ similar to db/db but
not as severe.
↳ high levels of leptin in
plasma





Leptin deficiency

Farooqui, I. S., et. al. (2002) J. Clin. Invest 110:1093-1103

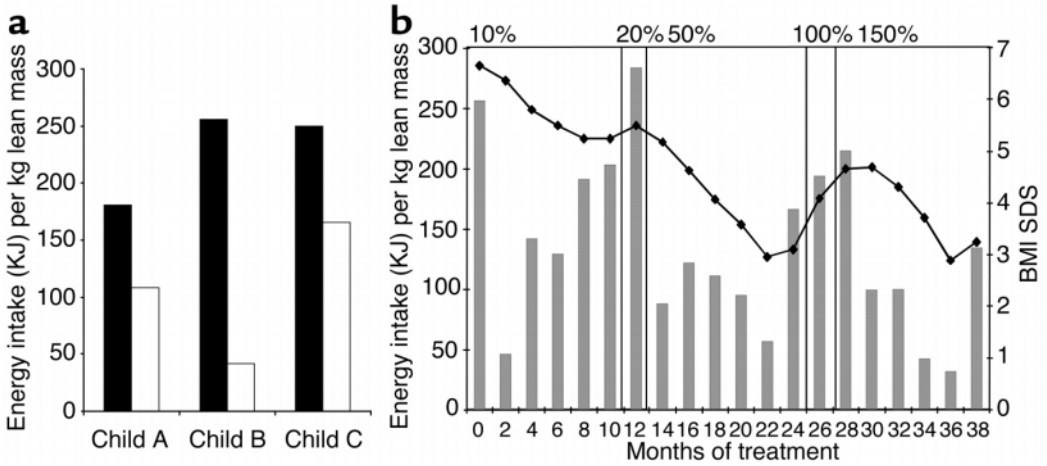
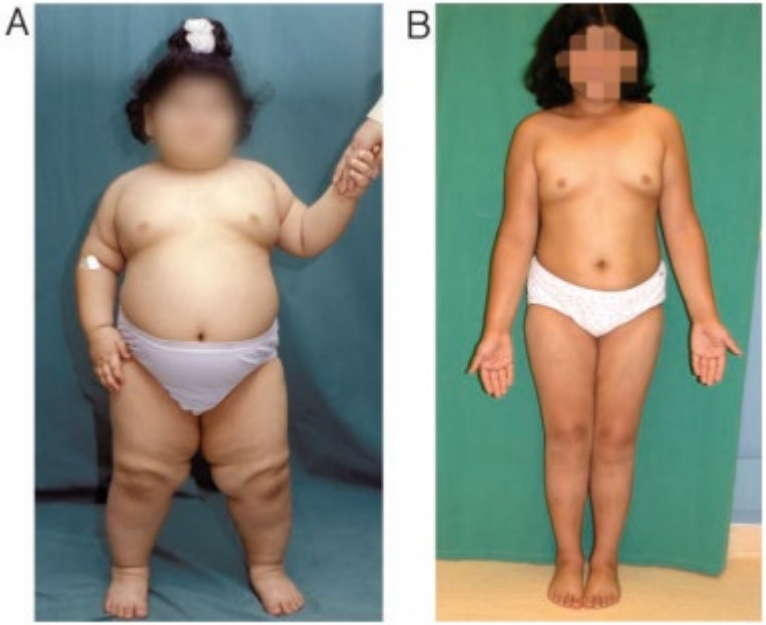


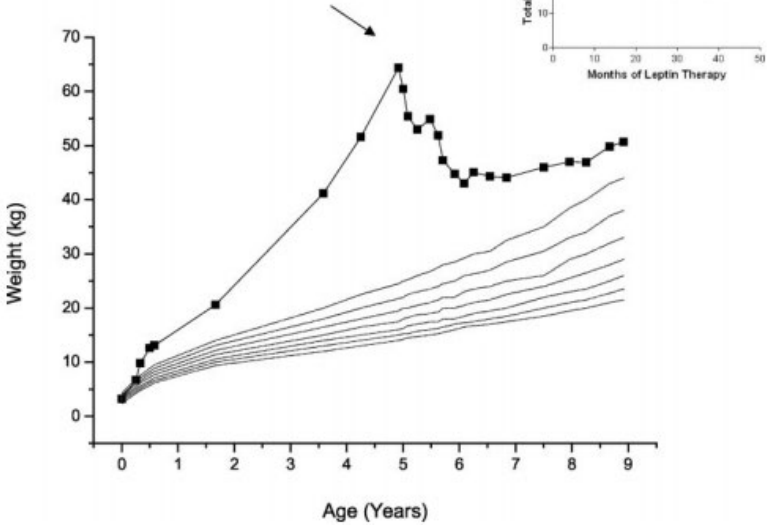
Figure 2

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.

Farooqui, I. S., et. al. (2002) J. Clin. Invest 110:1093-1103



Weight curve for the proband compared with normal percentiles for girls. Initiation of leptin therapy is marked by an arrow.



Gibson, W. T., et al. (2004) J. Clinical Endocrinology & Metabolism 89(10):4821-4826

Table 1. Summary of the effects of leptin replacement therapy

Endocrine effects	Reversal of type 2 diabetes
	Increase in insulin sensitivity; decrease in insulin secretion and in hepatic extraction
	Reversal of hypogonadotropic hypogonadism
	Increase in 24-h cortisolemia, with changes in rhythmicity towards a more regular pattern
	Increase in insulin-like growth factor binding protein (IGFBP1) and insulin-like growth factor binding protein (IGFBP2)
	Maintenance of adequate growth velocity*
	Regulation of the thyroid-stimulating hormone (TSH) rhythmicity
Body composition	Weight loss, mostly fat – up to 54% of initial body weight
Brain and behaviour	Decrease in caloric intake, with changes in food preference
	Increase in physical activity
	Increase in grey matter concentration
	Activation of brain areas involved with satiety and inhibition of areas involved with hunger
	Increase in cognitive development*
	Changes from docile and infantile to assertive and adult-like behaviour
Metabolic effects	Lower decrease in energy expenditure after weight loss
	Decrease in triglycerides and increase in high-density lipoprotein cholesterol (HDL-c)
	Inhibition of lipogenesis and stimulation of lipolysis
Biomarkers of inflammation, coagulation, fibrinolysis and platelet aggregation	Leptin withdrawal: changes towards a decreased state of thrombogenesis and increased fibrinolysis
Immunity	Decrease in the absolute lymphocyte count (CD3, CD4, CD19 cells)*
	Increased T-cell responsiveness*

* 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 lipotoxicity.

Gibson, W. T., et al. (2004) J. Clinical Endocrinology & Metabolism 89(10):4821-4826

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] Chizo Agwu,[5] Veronica Sanna,[2] Susan A. Jebb,[6] Francesco Perna,[7] Silvia Fontana,[2] Robert I. Lechler,[3] Alex M. DePaoli,[4] and Stephen O'Rahilly[1]

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[5]Department of Paediatrics, Sandwell Hospital, West Midlands, United Kingdom
[6]Medical Research Council, Human Nutrition Research, Cambridge, United Kingdom
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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 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.

This article was published online in advance of the print edition. The date of publication is available from the JCI website, http://www.jci.org. *J. Clin. Invest.* **110**:1093–1103 (2002). doi:10.1172/JCI200215693.

Farooqui, I. S., et. al. (2002) J. Clin. Invest 110:1093-1103

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The Journal of Clinical Endocrinology & Metabolism 89(10):4821–4826

doi: 10.1210/jc.2004-0376

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 ($Arg^{105}Trp$), 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 T_4 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)

Gibson, W. T., et al. (2004) J. Clinical Endocrinology & Metabolism 89(10):4821-4826

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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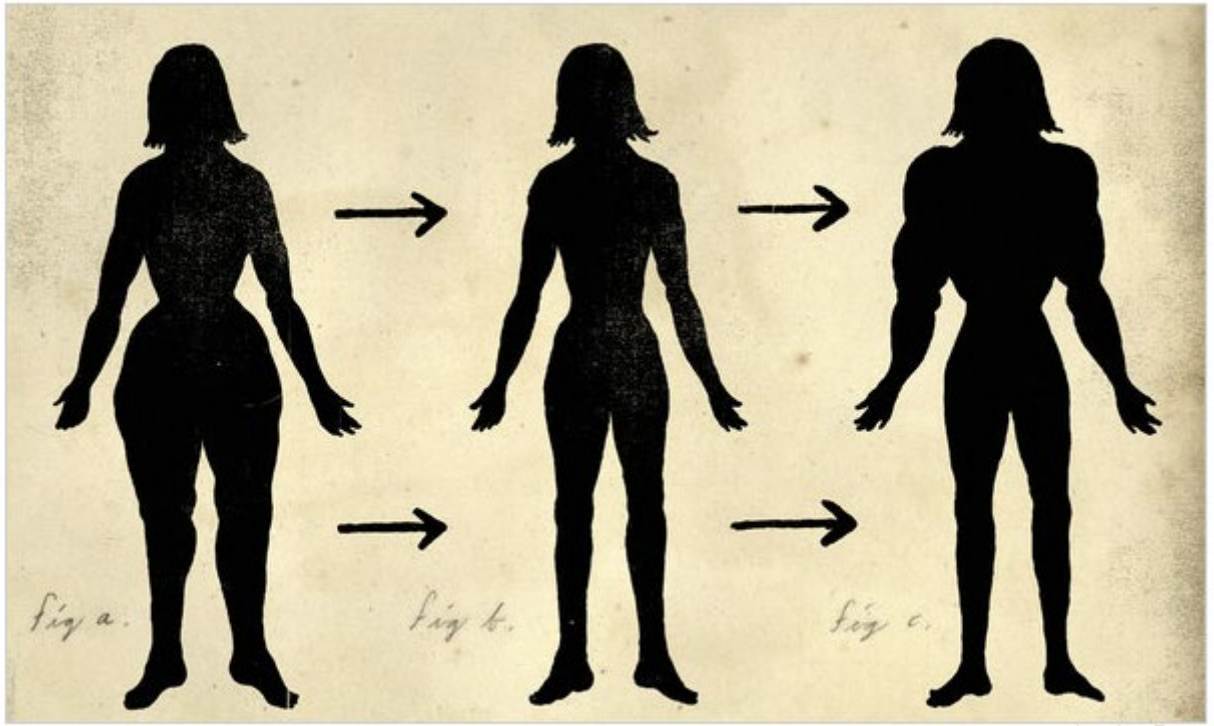
Summary

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 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.

obesity reviews (2011) **12**, e315–e323

With Liposuction, the Belly Finds What the Thighs Lose



Jonathon Rosen

By GINA KOLATA
Published: April 30, 2011