LEPTIN- AN ENERGY BAROMETER AND NEUROENDOCRINAL REGULATOR!!

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Is Obesity really *caused only due to greed, laziness* or a lack of willpower to exercise?
OVERVIEW

- INTRODUCTION
- SOURCES OF LEPTIN
- CENTRAL AND PERIPHERAL EFFECTS OF LEPTIN
- CLINICAL IMPLICATIONS
- OBESITY - A LEPTIN PARADOX !!
- M.C.Q’s
INTRODUCTION

Human leptin is a protein of 167 amino acids with a four-helix bundle motif similar to that of a cytokine.
INTRODUCTION

- Leptin (Greek – leptos) means thin

- It is a protein hormone that plays a key role in regulating energy intake and energy expenditure

- It is one of the most important adipose derived hormones

- The *Ob (Lep)* gene (*Ob* for obese, *Lep* for leptin) is located on chromosome 7 in humans
DISCOVERY

The effects of leptin were observed by studying mutant obese mice within a mouse colony at the Jackson Laboratory in 1950.

Leptin was discovered in 1994 by Jeffrey M. Friedman and Douglas L. Coleman through the study of such mice at Rockefeller University.
SOURCES OF LEPTIN

Major source of leptin is **white adipose tissue**
can also be produced by

- brown adipose tissue
- placenta
- ovaries
- skeletal muscle
- stomach
- mammary epithelial cells
- bone marrow
- pituitary
Leptin interacts with six types of receptors:

- $Ob-Ra$ to $Ob-Rf$
- encoded by a single gene, $LEPR$
- $Ob-Ra$ and $Rc$ → transport leptin across BBB
- $Ob-Rb$ → Hypothalamus, regulates energy homeostasis and neuroendocrine function
- $Ob-Re$ → binds circulating leptin
Once leptin has bound to the Ob-Rb receptor, it activates the JAK-stat, which is phosphorylated and travels to the nucleus to effect changes in gene expression.
CENTRAL AND PERIPHERAL EFFECTS OF LEPTIN
CENTRAL EFFECTS OF LEPTIN
Leptin binds to its receptor (expressed primarily in hypothalamus)

Hypothalamus modulates food intake and energy expenditure
LEPTIN - AN INDICATOR OF ENERGY BALANCE

When low leptin levels are detected by brain, the body is warned of limited energy supplies.

If high leptin levels are detected, the hypothalamus senses the body as being overweight.

This then triggers the body to eat less and expend more energy.
Leptin is a hormone produced by fat cells that regulates appetite. It is released into the bloodstream and travels to the hypothalamus, where it affects the appetite center, reducing the desire to eat. This process helps to maintain a healthy body weight. When leptin levels are low, the hypothalamus responds by increasing hunger signals, leading to overeating and weight gain. Conversely, when leptin levels are high, the hypothalamus receives the signal to decrease appetite and reduce food intake, promoting weight loss.
PEPTIDES THAT INCREASE FOOD INTAKE

- Orexin (lateral hypothalamus)
- NPY (arcuate and PVN)
- AgRP (arcuate and PVN)
- MCH (lateral hypothalamus)
PEPTIDES THAT DECREASE FOOD INTAKE

- POMC (αMSH) (arcuate and PVN)
- CART (arcuate nucleus)
- CRH (PVN)
LEPTIN SENSITIVE NEURONES

- Contained within the hypothalamus
- One of these subsets expresses NPY and AgRP, peptides that stimulate food intake and inhibit energy expenditure, thereby promoting positive energy balance.
- These NPY/AgRP neurons are inhibited by both leptin and insulin.
POMC neurons are stimulated by leptin

POMC

α-MSH

Inhibit food intake
increase energy expenditure and
promote weight loss
What Does Leptin Do?

Fat → More → Leptin → Hypothalamus 

↓ NPY, AgRP, ↑ POMC released → ↓ appetite, ↑ satiety

Less → Leptin → Hypothalamus 

↑ NPY, AgRP, ↓ POMC → ↑ appetite, ↓ satiety

Fat

VM, Arcuate Nucleus
PERIPHERAL EFFECTS

- Reproductive system
- Immune system
- Bone metabolism
- Circulatory system
- Glucose homeostasis
- Obesity and weight loss
EFFECT ON REPRODUCTIVE SYSTEM

LEPTIN

\[ \downarrow \]

Kisspeptin

\[ \downarrow \]

↑ Release of GnRH

\[ \downarrow \]

↑ LH, FSH and Testosterone
EFFECT ON REPRODUCTIVE SYSTEM (contd.)

- Leptin regulates reproductive functions by activating neurons that project afferent input to GnRH neurons in the preoptic area and other hypothalamic areas.

- Several neurons involved in energy homeostasis are anatomically associated with GnRH neurons (e.g., Ag RP, NPY and POMC neurons) and may thus link changes in energy balance with subsequent alterations in energy balance with subsequent alterations in reproductive function.
EFFECT ON REPRODUCTIVE SYSTEM (contd.)

- Leptin administration normalizes LH levels in females and restores testosterone level in males.

- Normal leptin levels may have a permissive role and thus be necessary for normal progression of puberty and reproductive maturity.
EFFECT ON HYPOTHALAMIC-PITUITARY-THYROID AXIS

- Leptin directly stimulates neurons in PVN of the hypothalamus to upregulate pro-TRH gene expression.

- Indirectly influences TRH neurons in the PVN through signals from the arcuate nucleus.
EFFECT ON HYPOTHALAMIC-PITUITARY-THYROID AXIS

- TSH and Leptin secreted in a pulsatile fashion

- Congenital leptin deficiency

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  Highly disorganized TSH secretion pattern

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  Induce changes on metabolism
EFFECT ON HYPOTHALAMIC-PITUITARY-GROWTH HORMONE AXIS

Leptin

↓

GHRH

↓

Increase in GH secretion
In humans, leptin may regulate not GH secretion per se but mainly the effect of GH to regulate secretion of IGF-I and its binding proteins in the periphery.
EFFECT ON HYPOTHALAMO - PITUITARY - ADRENAL AXIS

Leptin

stimulation of CRH release

increase in ACTH and cortisol
EFFECT ON CIRCULATORY SYSTEM

The role of leptin/leptin receptors in modulation of T cell activity in immune system was shown in experimentation with mice.

Exogenous leptin can promote angiogenesis by increasing vascular endothelial growth factor levels.
Adipocytes release leptin, which travels to the hypothalamus. In the hypothalamus, leptin can act in an endocrine or paracrine manner. Endocrine action of leptin increases VEGF, leading to increased vascular permeability and angiogenesis. Paracrine action of leptin, through Ob-Rb on ECs, also results in angiogenesis. This leads to decreased food intake.
LEPTIN AND NITRIC OXIDE

- Leptin can modulate vascular tone through local mechanisms involving nitric oxide (NO) release mediated through Endothelial Nitric Oxide Synthase Phosphorylation pathway.
EFFECT ON BONE METABOLISM

Leptin decreases cancellous bone, but increases cortical bone. This "cortical-cancellous dichotomy" may represent a mechanism for enlarging bone size, and thus bone resistance to cope with increased body weight.
EFFECT ON BONE METABOLISM (contd.)

Direct effects of leptin in bone

In vitro studies and systemic administration

Leptin binds to receptors on osteoblasts

Osteoblast differentiation and activity

Osteoclast activity

Bone Mass
There is a potential for treatment of diseases of bone formation - such as impaired fracture healing – with leptin.
EFFECT ON IMMUNE FUNCTION

Leptin:
- enhance phagocytic activity in macrophages
- promote production of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-12
- stimulate chemotaxis in polymorphonuclear cells
- promotes lymphocyte survival in-vitro by suppressing Fas-mediated apoptosis

Hypoleptinemic states → increased risk of infection
EFFECT ON GLUCOSE METABOLISM

- Growing evidence implicates leptin in glucose homeostasis as well, particularly in the control of peripheral tissue insulin sensitivity.

- Mice with genetic leptin deficiency or leptin receptor deficiency exhibited not only hyperphagia and obesity, but insulin resistance and diabetes as well.
Findings suggest that hypothalamic leptin signaling is an important determinant of glucose metabolism and that the underlying neuronal mechanism involves Phosphatidylinositol-3 kinase (PI3K) signaling.
INDIRECT EFFECTS OF LEPTIN ON GLUCOSE METABOLISM

- Effects on lipid metabolism

- Decreases intracellular lipid concentration through reduction of fatty acid and triglyceride synthesis and a concomitant increase in lipid oxidation
EFFECT ON GLUCOSE METABOLISM (contd.)

Leptin treatment restores euglycemia and normalizes peripheral insulin sensitivity in animal models of type-I diabetes.
CLINICAL APPLICATIONS:
Leptin replacement has been studied in:

- Congenital leptin deficiency
- Lipodystrophy
- Hypothalamic amenorrhoea
CONGENITAL LEPTIN DEFICIENCY

- marked obesity (hyperphagia)
- hypogonadotrophic hypogonadism (inadequate secretion of GnRH)
- failure to reach puberty, including absence of growth spurt, secondary sex characteristics and menarche

Leptin replacement reverses several of the changes seen with congenital leptin deficiency
LIPODYSTROPHY

- Loss of subcutaneous adipose tissue
- Increase in visceral adipose tissue
- It is a rare autosomal recessive condition

Leptin replacement therapy dramatically improves dyslipidemia and insulin sensitivity in these individuals and reduces hepatic gluconeogenesis and intrahepatic fat content
HYPOTHALAMIC AMENORRHOEA

- Common cause of **absent menstrual periods** and **infertility**

- Leptin may be a promising treatment for **infertility** in women with **hypothalamic amenorrhoea**

- Leptin can **normalize LH concentrations** and pulse frequency within **weeks** of treatment and can **restore ovulatory function** after only **months** of treatment
Leptin is a hormone that is produced by the body’s fat cells.

It is often referred to as the “satiety hormone” or the “starvation hormone”.

Leptin’s primary target is in the brain, particularly an area called the hypothalamus.

Various Central and Peripheral effects.
Leptin is *supposed* to tell the brain that we have enough fat stored, that we don’t need to eat, and that we can burn calories at a normal rate.

- We eat → body fat goes up → leptin goes up → we eat less and burn more.
- Or...
- We don’t eat → body fat goes down → leptin goes down → we eat more and burn less.
PARADOX OF LEPTIN- OBESITY !!

- Obese have a lot of body fat in their fat cells.
- Very high levels of leptin.
- People shouldn’t be eating... their brain should know that they have plenty of energy stored.
PARADOX OF LEPTIN- OBESITY !!

- There’s a whole ton of leptin floating around, but the brain doesn’t “see” that it is there.

- Leptin resistance- It is now believed to be the main biological abnormality in human obesity

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  Change our physiology and behavior in order to regain the fat that the brain thinks we’re missing.
LEPTIN RESISTANCE

- Hunger and reduced energy expenditure.
PARADOX OF LEPTIN-OBESITY
Genes → Insulin Resistance → IG/DM2 → Atherosclerosis

Lifestyle → Cytokine Imbalance → FFA

- Dyslipidemia: ↓ HDL-C
- Small LDL-C: ↑ Triglycerides
- HBP
- ↓ Thrombolysis
- Endothelial Dysfunction
- Inflammation

Atherosclerosis
WEIGHT LOSS DIETS

Most “diets” don’t provide good long-term results. This is a well known problem in weight loss studies.

Significant reduction in leptin levels

Brain doesn’t necessarily reverse its leptin resistance.

Hunger, increased appetite, reduced motivation to exercise and decreased amount of calories burned at rest
LEPTIN RESISTANCE

- Leptin resistance or tolerance was first thought to be due to mutations of the leptin receptor and other rare monogenic obesity syndromes.

- Leptin transport across the blood-brain barrier is impaired in obesity. This is partially due to saturation of the transporter as a result of hyperleptinemia and a subsequent decrease in transport activity.
LEPTIN RESISTANCE

- Endoplasmic reticulum stress in the liver, adipose tissue, and pancreatic β-cells has recently been shown to play a role in the development of leptin resistance.
LEPTIN RESISTANCE

- Targeting these mechanisms of leptin resistance has led to development of leptin sensitizers.

- **Amylin** may act synergistically with leptin to induce fat-specific weight loss, and the amylin analog pramlintide has been tried in conjunction with leptin in clinical trials for weight loss with modest effects.
CELLULAR MECHANISMS BEHIND LEPTIN RESISTANCE

- **Inflammation:** Inflammatory signaling in the hypothalamus (IL-6, IL-8, IL-10, TNF-α, FABP4)

- **Free Fatty Acids:** Having elevated free fatty acids in the bloodstream may increase fat metabolites in the brain and interfere with leptin signaling.

- **Having high leptin:** Having elevated levels of leptin in the first place seems to cause leptin resistance.
WHAT SCIENCE KNOWS ABOUT REVERSING LEPTIN RESISTANCE?

- The best way to know if one is leptin resistant, is to look in the mirror
REVERSING LEPTIN RESISTANCE

- If there is a lot of body fat, especially in the belly area, then one is almost certainly leptin resistant.

- A key to preventing (or reversing) leptin resistance, is reducing diet-induced inflammation.
REVERSING LEPTIN RESISTANCE

- **Avoid processed food:** Highly processed foods (foods high in sugar, refined flour and vegetable oils) may compromise the integrity of the gut and drive to inflammation.

- **Eat Soluble Fiber:** Eating soluble fiber can help improve gut health and may protect against obesity.
REVERSING LEPTIN RESISTANCE

- **Sleep:** Poor sleep has been implicated in problems with leptin.

- **Lower your triglycerides:** Having high blood triglycerides can prevent the transport of leptin from blood and into the brain. The best way to lower triglycerides is to reduce carbohydrate intake.

- **Eat Protein:** Eating plenty of protein can cause automatic weight loss. There are many reasons for that, one of them may be an improvement in leptin sensitivity.
**REVERSING LEPTIN RESISTANCE**

- **Exercise:** Physical activity may help to reverse leptin resistance.

- The effect of long-term exercise training on leptin concentration has shown that regular exercise allows “resetting” of the leptin concentration so that a lower concentration can be maintained at a certain body fat content.

- Physical activity is known to increase sympathetic nerve activity that promotes down-regulation of plasma leptin concentrations.
REVERSING LEPTIN RESISTANCE

Regular exercise helps you to have a better night’s sleep.

Exercise  Nutrition  Sleep
Chronic stress is a multi-pronged dagger that has felled many. Unmitigated stress increases cortisol levels directly interferes with how leptin functions.


Mindful eating is considered a form of meditation and is associated with decreased craving for food, improved sugar control, feeding behavior, and weight management.
NUTRACEUTICAL “FOOD AS MEDICINE” APPROACHES

- **Curcumin** from turmeric downregulates leptin.

- **Omega 3 fatty acids** found in fish, nuts, seeds, and some plants may help modulate release of leptin.

- **Probiotics** improve gastrointestinal integrity and immune balance, improving production of short chain fatty acids which will have direct influence on leptin.

- **Aloe leaf, licorice extract, vitamin D, ginger, garlic, green tea extract** offer positive benefits on gut bacteria, **gut-brain interactions** and general immune health.
REVERSING LEPTIN RESISTANCE

- Unfortunately, there is no simple way to do this!!

- Eating **real food** (not modern processed foods high in **sugar** i.e. fructose, refined flour and vegetable oils), maintaining a healthy gut, exercising, sleeping well, mind-body practices etc...

- **Drastic shift in lifestyle with all interventions.**
TAKE HOME MESSAGE

- Obesity is **not caused by only greed, laziness or a lack of willpower**

- There are **strong biochemical forces** at play... which promote increased hunger and decrease energy consumption.

- Individual is still responsible to help oneself.
TAKE HOME MESSAGE

Although the causes of obesity are complicated and diverse, leptin resistance is the main reason.

Drastic shift in lifestyle.
CONCLUSION

- Regulation of leptin in the body will have a profound impact on the treatment of obesity, diabetes mellitus and infertility.
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References


Thank you
MCQ’s

1) Major source of leptin is:

a. White adipose tissue
b. Skeletal muscle
c. Liver
d. Ovary
MCQ’s

Leptin is also known as:

a. Satiety hormone
b. Starvation hormone
c. Both the above
d. None of the above
MCQ’s

Mechanisms behind leptin resistance:

a. Inflammation
b. Free fatty acids
c. High leptin levels
d. All the above
MCQ’s

Effect of Leptin on glucose metabolism:

a. ↑ses hepatic glucose production and glucose utilization in muscles
b. ↓ses hepatic glucose production and glucose utilization in muscles
c. ↓ses hepatic glucose production and ↑ses glucose utilization in muscles
d. None of the above
MCQ’s

Peptides which decrease food intake:

a. Proopiomelanocortin (POMC)
b. Orexin
c. Agouti related peptide (AgRP)
d. Neuropeptide Y (NPY)