Leptin and the Central Nervous System Control of Glucose Metabolism

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Insulin and Leptin: The Big Picture

Leptin

Excess Glucose

Insulin
Leptin: the “Satiety Hormone”

- Leptin is a hormone that helps regulate energy homeostasis by inhibiting hunger and increasing energy expenditure.
- Leptin is produced primarily in the adipocytes of white adipose tissue, but also in brown adipose tissue and other locations.
- In the Hypothalamus, leptin receptors are found in ARC (arcuate nucleus), Ventromedial Nucleus (VMN), and Dorsomedial Nucleus (DMN), with some expression in Paraventricular Nucleus (PVN), and Lateral Hypothalamic Area (LHA).
- Leptin is also expressed in Hippocampus, Hindbrain, Ventral Tegmental area (mesolimbic reward areas), substantia nigra, and olfactory processing areas.
Leptin Effects

- Reduces food intake by inhibiting hunger, which results in lower body weight
- Regulates energy balance by increasing energy expenditure
- Controls glucose metabolism by enhancing insulin’s ability to suppress glucose production via an unknown mechanism.
Mice Studies

• When a normal mouse colony gave birth to a generation of massively obese mice, it was thought that there was a mutation in a gene that regulates hunger and energy expenditure. The Jackson Lab called this gene \textit{ob} (for obese)
• In 1953, Kennedy hypothesized that body adiposity was regulated by circulating factors released in proportion to adipose tissue mass that acted in the brain to maintain energy balance.
• A second mutation that resulted in a similar phenotype was discovered and named \textit{db} (for diabetic)
• in 1994, Zhang et al successfully identified and cloned the \textit{ob} gene and showed that it is expressed selectively in adipose tissue and encodes a peptide hormone “leptin.”
**ob/ob Mice**

- *ob* gene codes for the protein Leptin.
- A mice mutant for the gene cannot produce leptin, leading to uncontrolled hunger.
**db/db Mice**

- *db* gene codes for the leptin receptors
- A mice mutant for the gene cannot create leptin receptors
Leptin Resistance

- Leptin is released proportionally to body adiposity
- Increased adiposity levels causes increased plasma leptin concentration → Chronic overstimulation of the leptin receptor causes leptin resistance
- Leptin resistance leads to increased body adiposity → Negative energy balance compromised
Lipodystrophy

• Characterized by abnormal or degenerative conditions of the body's adipose tissue

• Congenital generalized lipodystrophy (CGL)—condition in which body fat is absent from birth

• Familial partial Lipodystrophy (FPL)—the loss of body fat is progressive and variable, occurring during childhood and puberty
The JAK-STAT Pathway LepRb

- Tyrosine 985
- Tyrosine 1077
- Tyrosine 1138
- JAK-2
- Phosphate Group

Food Intake
Importance of Tyrosine Residues on LepRb

Tyrosine 985 mutant (ll)
Lean phenotype and reduced adiposity
Tyr 985 important for reduction of LepRb activity through SOCS inhibition

SOCS3 Mutant
“Resistant to obesity” because mice display higher leptin sensitivity

Tyrosine 1138 mutant (ss)
Hyperphagia, obese phenotype, and reduced energy expenditure
Tyr 1138 important for regulation of energy homeostasis through recruitment of STAT3
IRS-PI3K Pathway LepRb and IR

- Tyrosine 985
- Tyrosine 1077
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- JAK-2
- PI3K
- Insulin
- Phosphate Group
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Leptin and the Hypothalamus
The POMC cleavage product alpha-melanocyte stimulating hormone (α-MSH) is released by these neurons and acts on melanocortin receptors (Mc3r/Mc4r) to inhibit food intake, increase energy expenditure, and promote weight loss, therefore functioning as negative energy balance.

Leptin and insulin act in distinct subpopulations of POMC cells, rather than acting on the same subset of POMC cells.

- INSULIN: hyperpolarizes and silences POMC neurons and activates PI3K signaling in these neurons
- LEPTIN: activates POMC neurons and activates PI3K signaling in these cells

The subset of POMC cells in which leptin-induced c-fos activity is detected is separate from those POMC neurons that express the insulin receptor
NPY and AgRP Neurons

- Neuropeptide Y (NPY) and Agouti Related Peptide (AgRP) are peptides that stimulate food intake and inhibit energy expenditure, thereby promoting positive energy balance.
  - NPY/AgRP activate the Y1 and Y5 receptors and reduce melanocortin signaling.
  - They release GABA and inhibit POMC neurons
- As these NPY/AgRP neurons are inhibited by both leptin and insulin, reduced neuronal input from these hormones increases hypothalamic expression of these peptides.
  - LEPTIN: leptin inhibits the firing rate of NPY/AgRP neurons
  - INSULIN: activates PI3K signaling in AgRP cells but inhibits these cells from firing
Nutrient Sensing

Eat More!  
Increased Fat Oxidation
Concluding Remarks

- Both leptin and insulin have effects that involve a shared pathway (IRS / PI3K).
- Leptin and insulin act on different subsets of neurons that have different effects.
- Leptin affects glucose levels mainly through affecting production rather than glucose uptake.
- Leptin also affects energy homeostasis through a mechanism distinct from its effect on glucose homeostasis.