Leptin & Glucose Metabolism

Bree Sarkisian & Kelsey Krug
Overview

• IA CNS Control of Glucose Homeostasis
• IB Adiposity Signals: Insulin & Leptin
• IIA JakSTAT Pathway
• IIB IRS-PI3K Pathway
• IIIA Leptin & Glucose Metabolism
• IIIB CNS Sites & Mechanisms of Leptin Action
• IIIC Role of Hypothalamic PI3K→ review from insulin lecture
• IIID CNS Nutrient Sensing
• IIIE Leptin-Sensitive Neuronal Subsets
• IIIF Effect of CNS Leptin on Glucose Metabolism
• IIIG Neurocircuits for Leptin Reg of Insulin Sensitivity
• IIIH Indirect Effects of CNS Leptin on Glucose Metabolism
• VA Leptin Resistance
• VB Physiological Relevance
• VI Conclusions
Leptin Basics
-Maintains the body’s normal energy balance
-Increased leptin will decrease food intake and increase energy expenditure
-Levels are proportional to body fat (adipose tissue)
-Can act to increase OR decrease plasma glucose depending on body’s needs
IA /IB: Insulin and Leptin: CNS Control of Glucose Metabolism

• Insulin and Leptin give info to CNS about long term energy stores

• Ob gene: in adipose: encodes leptin
  –Ob/ob mice have obesity, leptin administration in CSF= reduced food intake and body weight
  –In humans subjected to weight loss, admin of leptin blocks reduction of SNS (encourages weight gain)
IIA- JakSTAT pathway

- Leptin Receptor=LepRb
- If you replace Tyrosine with serine:
  - $985 \rightarrow$ Decrease food intake, decrease adiposity, increase leptin sensitivity (no SOCS binding.
  - $1077 \rightarrow$ Never tried! But we know STAT5 is important
  - $1138 \rightarrow$ no STAT3= hyperphagia, Decrease energy expen.
- JAK phos-Independent pathway: truncate LepRb: we see delayed diabetes progression but all else remains the same
IIB: IRS PI3K Pathway

- Convergence of leptin and insulin?
  - Inhibition of PI3K = inhibition of leptin and insulin action on hypothalamus
- Both AFFECT glucose responsive neurons in ARC via kATP (there are different subsets with diff responses)
- SH2B1: facilitates Jak2 mediated IRS phosphorylation in response to LepRb activation
  - SH2B1 has been ID’d as obesity risk allele in humans
III A: Leptin and Glucose Metabolism

• At least two distinct ways leptin helps glucose regulation:
  1) Energy balance (food intake, expenditure)
  2) direct action on tissues/ genes
    – Leptin administration fixes hyperglycemia and hyperinsulinemia even when diffs in food intake are controlled

Model: lipodystrophy = low leptin

– Leptin therapy seems to preferentially help insulin signaling in liver (not other tissues) so it alone cannot normalize glucose
– Glucagon (enzyme for gluconeogenesis) signaling is required for hyperglycemia and leptin is involved in decrease of blood glucagon
IIIB: CNS Sites and Mechs of Leptin Action

What Leptin does:
- suppresses hepatic glycogenolysis
- inhibits hepatic gluconeogenesis
- Enhances insulin prevention of glucose production without affecting (and sometimes even improving) insulin dependent glucose uptake
- Can do this even in the face of severe insulin deficiency

Where Leptin is found:
- ARC, VMH, DMN
- Block all receptors, then selectively reactivate → ARC is the big player for leptin signaling effect on glucose independent of energy management
- if we inhibit PI3K ARC loses its effects
IIIE: Leptin-Sensitive Neurons

Arcuate nucleus (ARC):

1) NPY expressing: Stimulate food intake and inhibit energy expenditure (inhibited by leptin and insulin)

2) POMC: inhibit food intake, increase energy expenditure (stimulated by leptin, insulin mixed effects)
   • Contradictory effects- possible subpopulations for insulin vs leptin

Ventromedial Hypothalamus (VMH):

• Leptin increases firing of steroidogenic factor (SF-1)→ promotes glucose uptake in tissues via SNS

• VMH is also implicated in glucagon secretion (we established ins section IIIA that leptin is involved in glucagon signaling)
IIIF: Effect of CNS Leptin on Glucose Metabolism

- **Leptin affects gluconeogenesis** through melanocortin pathway (MSH, also involved with insulin signaling) and **inhibits glycogenolysis** through a separate, melanocortin-independent pathway.

- **Influences hepatic genes and insulin** to reduce glucose production and increase glucose use
  - Inhibits SCD1 (lipogenesis) → alters insulin sensitivity
  - Upregulates IGFB2 (reduces blood glucose through increased insulin sensitivity)
Figure 23-36
Lehninger Principles of Biochemistry, Fifth Edition
IIIG: Neurocircuits for Leptin Reg of Insulin Sensitivity
IIIH: Indirect Effects

Weight loss as little as 5-10% improves insulin sensitivity

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<thead>
<tr>
<th>Leptin Effect</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>-Regulate food intake</td>
<td>STAT3 signaling</td>
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<td>-Glucose metabolism</td>
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<tr>
<td>-Reproductive function</td>
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<td>-Adipose tissue metabolism</td>
<td>Hypothalamic PI3K and SNS outflow</td>
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<td>-Energy regulation</td>
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Leptin resistance can develop much the same as insulin resistance (Peter and the wolf)
Conclusions

- Leptin and insulin have overlapping effects and may involve similar mechanisms (IRS PI3K signaling) but they act on different subsets of neurons and have varying effects based on physiological context.
- Leptin influences glucose production (often by effects on insulin and hepatic gene expression) more than glucose uptake.
- Leptin has effects on energy maintenance and glucose metabolism through separate and distinct mechanisms, most of which require further study to be fully understood.