Insulin-Leptin Interactions

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‘If you understand a system, you can predict it.’
Agenda

- Energy homeostasis
- Overview of leptin and insulin
- Signaling pathways and interactions
- Pathway impairments
- Brain region-Hormone effects
- Review of existing research
- Future directions
- Summary/questions
Leptin Signaling Pathway

Adipose and other tissues
Leptin
Leptin binds to receptor
PI3K
Activation of PI3K enzyme
JAK2
STAT3
Phosphorylation of JAK2 and STAT3
SOCS3 inhibits production
SOCS3 is activated
STAT3 crosses membrane

Leptin binds to receptor LepRb
Leptin
PI3K
IRS

Insulin binds to receptor

Activation of PI3K enzyme

Conversion of PIP2 to PIP3

PDK1 phosphorylates AKT

AKT crosses membrane

Phosphorylation of FOXO1 causes it to leave

SOCS3 inhibits production

Expected response of appetite suppression
Interactions between pathways

- Both leptin and insulin have anorexigenic effects
  - phosphorylation of JAK2 and subsequent pathways
  - Stimulation of POMC neurons
Leptin-Insulin in the brain

Blood-brain barrier: saturable transport system

- Impaired leptin transport across the barrier with obesity
  - Leptin resistance
- Impaired insulin transport across the barrier with hyperinsulinemia
  - Insulin resistance
- Insulin can increase transport of leptin across BBB
Leptin-Insulin in the Hypothalamus

- Leptin and leptin receptor (LEPR) neurons
  - **Arcuate nucleus:** Upregulates POMC/CART neurons, downregulates AgRP/NPY neurons
    - ↓↓↓ food intake, ↓↓↓ body weight
    - ↑↑↑ energy expenditure
  - **Ventromedial:** stimulates SF1 neurons
    - ↓↓↓ feeding
  - **Lateral hypothalamic area:** downregulates orexin and MCH neurons
    - ↓↓↓ feeding
Leptin-Insulin in the Hypothalamus

- Insulin and insulin receptor (IR) neurons
  - **AKT pathway** inactivates FOXO1 transcription factor
  - FOXO1:
    - ↑↑↑ Orexigenic neuropeptides
    - ↓↓↓ Anorexigenic peptides
  - Overexpression of FOXO1 → obesity, glucose intolerance
Pathway Impairments

Case 1: SOCS3
Case 2: SH2b1
Case 3: POMC
Pathway Impairments Cont.

Larger Implications:
- Leptin Signaling deficiencies and memory
- Melanocortin Signaling: obese, pale skinned phenotypes
SnapShot: Neural Pathways that Control Feeding

- **POMC**
- **AGRP**
- **Insulin**
- **Leptin**
- **Ghrelin**
- **5HT**

The diagram illustrates the neural pathways involved in controlling feeding behavior, with key neuropeptides and hormones such as POMC, AGRP, Insulin, Leptin, Ghrelin, and 5HT, and their interactions with the PV and PVH regions of the brain.
Effects in Hippocampus

- Synaptic potential gets messed up because of leptin resistance
  - Obesity & hyperleptinemia → damage synaptic transmission process = leptin activity weakened
- But, leptin can ↑ potentiation → change in synaptic plasticity and aspects of learning and memory
  - Mechanics: Leptin + NMDA receptors
    - Mediated by PI3K & MAPK
Effects in Cerebral Cortex

- Lesions here modify feeding
- Changes in JAK/STAT pathway → decreased cortical activity
  - Evidence: JAK2 & STAT3 are less active in obese mice (hyperleptinemic + high serum insulin-level)
- MAPK/ERK pathway, some neurotransmitters, and synaptic plasticity affected by leptin & insulin
Effects in Cerebellum

- With ataxia, IR levels here ↓
- However, leptin + STAT3 in AgRP neurons → p-Tyr705-STAT3 levels stimulate locomotion
  - Leptin-deficient mice: less mobility
- Damage here: ↓ body weight
- So, highlights idea that leptin & insulin could affect cerebellum via STAT3
Obesity & hyperleptinemia → damage synaptic transmission process = leptin activity weakened & leptin can ↑ potentiation

Changes in JAK/STAT pathway → decreased cortical activity

leptin + STAT3 in AgRP neurons → p-Tyr705-STAT3 levels stimulate locomotion (even without insulin)
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<thead>
<tr>
<th>Study Name</th>
<th>Region</th>
<th>Relevant Players</th>
<th>Methods</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Fujikawa et al. 2013 -</td>
<td>VMH for SF1 cells, arcuate nucleus, lateral hypothalamic area, DMH</td>
<td>Leptin receptors (LEPRs) in POMC, SF1, and GABAergic neurons</td>
<td>Knocking out LEPRs in POMC, SF1, or GABAergic neurons in insulin deficient mice, and administering leptin treatment</td>
<td>Leptin + LEPRs in POMC neurons cannot sufficiently compensate for insulin deficiency; marginally lowers hyperglycemia</td>
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<td>Leptin Engages Hypothalamic Neurocircuitry ...</td>
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However, GABAergic neuron LEPRs + leptin reduce hyperglucagonemia + hyperglycemia, improve survival, esp when combined w/ POMC LEPRs
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<td>Irani et al. 2007 - <em>Altered hypothalamic leptin, insulin, melanocortin..</em></td>
<td>DMH, arcuate nucleus, dorsomedial VMH, VTA, hippocampus</td>
<td>Insulin, leptin, melanocortin and associated receptors</td>
<td>Breeding rats to develop diet induced obesity and diet resistance - fed each group high energy diet, measured receptor functioning</td>
<td>High energy diets in rats with genetic predisposition associated with reduced:</td>
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<td>-leptin hypothalamic binding,</td>
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<td>-hypothalamic melanocortin-3,-4 receptor binding,</td>
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<td>-and hippocampal insulin binding</td>
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<td>VTA binding unaffected</td>
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Thank you for listening! Questions to Consider

- Look into recyclable drugs which can be used as therapeutic benefits for patients with T2DM.
- Are there any underlying mechanisms other than what we have shown you which mandate homestatic inputs and outputs?
- Do we need insulin and leptin for cellular survival?
Take home message.

We suspect that the heterogeneity and plasticity of adipose tissue will be important themes over the next 10 years and that the field will aim to identify all the different types of adipocytes and their progenitors and investigate their differences. Understanding the function of these cell types and how or whether distinct subpopulations can differentiate into other cell types will be crucial. Ultimately, we will need a new set of biochemical and genetic tools to isolate and/or target individual subpopulations of adipocytes and progenitors in a depot-specific manner. Such complexity can be daunting, but achieving this will grant opportunity to develop new strategies and therapeutics for metabolic disease.
Acknowledgments

- COGS 163 Class (YOU GUYS)
- Dr. Boyle COGS 163 Foundation
- Google Drive Fruit Background

- FIGHT FOR ELSEVIER!
INSULIN–LEPTIN SIGNALING IN THE BRAIN

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Abstract: Energy homeostasis, a term used to designate the physiological processes that regulate the metabolic state, is controlled by different organs, including the brain. Leptin and insulin play a key role in the central control of feeding and body weight, with interconnected signaling pathways at various levels. In addition, central resistance to their actions has a primary role in the pathogenesis of obesity and type 2 diabetes. Studies performed in knockout mice for insulin targets show that the impairment of insulin signaling is related to changes in learning and memory. Moreover, circadian neurological alterations induce metabolic processes that lead to obesity and insulin resistance in patients with mental disorders. Thus, leptin and insulin signaling may be a link between the pathophysiological states affecting energy homeostasis and the appearance of mental illnesses. Pharmacological targeting for these signaling pathways could lead to important medical benefits in these diseases.

4.1 INTRODUCTION

This chapter first reviews the central regulation of food intake and energy balance. Brain insulin-leptin signaling mechanisms and the cross-talk between these hormones are described. Finally, some situations where metabolic disorders and neurodegenerative diseases associated with disturbances in leptin negative feedback mechanism between other control systems seems to be implicated. According to this idea, peripheral signals related to energy homeostasis are sensed by central structures to induce physiological outputs that modulate feeding and energy expenditure. In addition, behavioral outputs are also involved in this response. Thus, the availability of nutrients via leptin and insulin signaling is detected
Leptin signaling
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Abstract

Leptin is secreted by adipose tissue and regulates energy homeostasis, glucose and lipid metabolism, immune function, and other systems. The binding of leptin to its specific receptor activates various intracellular signaling pathways, including Janus kinase 2 (JAK2)/ signal transducer and activator of transcription 3 (STAT3), insulin receptor substrate (IRS)/phosphatidylinositol 3 kinase (PI3K), SH2-containing protein tyrosine phosphatase 2 (SHP2)/mitogen-activated protein kinase (MAPK), and 5' adenosine monophosphate-activated protein kinase (AMPK)/ acetyl-CoA carboxylase (ACC), in the central nervous system and peripheral tissues. Understanding of leptin signaling provides insights into its roles in health and disease.

Introduction

Leptin is primarily synthesized and secreted by white adipose tissue and an increase in overfed and obese states [2]. Leptin is secreted in a pulsatile fashion and also displays a
20 YEARS OF LEPTIN

Human disorders of leptin action

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Abstract
The discovery of leptin has provided a robust framework upon which our current understanding of the mechanisms involved in energy homeostasis has been built. In this review, we describe how the identification of humans with mutations in the genes encoding leptin and the leptin receptor and the characterisation of the associated clinical phenotypes have provided insights into the role of leptin-responsive pathways in the regulation of eating behaviour, intermediary metabolism and the onset of puberty. Importantly, administration of recombinant human leptin in leptin deficiency represents the first mechanistically based targeted therapy for obesity and has provided immense clinical benefits for the patients concerned. In subsequent years, we and others have shown that human obesity can result from a multiplicity of defects in the pathways downstream of leptin signalling within the brain.

Key Words
- leptin
- receptors
- obesity
- signal transduction

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Review

Leptin and its role in hippocampal synaptic plasticity

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Abstract

It is well documented that the hormone leptin plays a pivotal role in regulating food intake and body weight via its hypothalamic actions. However, leptin receptors are expressed throughout the brain with high levels found in the hippocampus. Evidence is accumulating that leptin has widespread actions on CNS function and in particular learning and memory. Recent studies have demonstrated that leptin-deficient or-insensitive rodents have impairments in hippocampal synaptic plasticity and in spatial memory tasks performed in the Morris water maze. Moreover, direct administration of leptin into the brain facilitates hippocampal long-term potentiation (LTP), and improves memory performance in mice. There is also evidence that, at the cellular level, leptin has the capacity to convert hippocampal short-term potentiation (STP) into LTP, via enhancing NMDA receptor function. Recent data indicates that leptin can also induce a novel form of NMDA receptor-dependent hippocampal long-term depression. Here, we review the evidence implicating a key role for the hormone leptin in modulating hippocampal synaptic plasticity and discuss the role of lipid signaling cascades in this process.

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Keywords: Leptin; NMDA receptor; Long-term potentiation; Long-term depression; Hippocampus; PI 3-kinase

Contents
Leptin Engages a Hypothalamic Neurocircuitry to Permit Survival in the Absence of Insulin

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SUMMARY

The dogma that life without insulin is incompatible has recently been challenged by results showing the viability of insulin-deficient rodents undergoing leptin monotherapy. Yet, the mechanisms underlying these actions of leptin are unknown. Here, the meta-

and type 2 diabetes mellitus (T2DM), or complete pancreatec-
tomy (Butler et al., 2007; Coppari and Bjorbaek, 2012; Talchai et al., 2012). If untreated, this defect leads to hyperglycemia, polyuria, ketoadidosis, and death. To date, insulin therapy is the only lifesaving intervention available to several millions of people suffering from insulin deficiency. Thus, daily insulin administrations and frequent glucose monitoring are quotidian aspects of modern diabetes management.
Rats with a genetic predisposition to develop diet-induced obesity (DIO) have a preexisting reduction in central leptin and insulin sensitivity. High-fat diets also reduce sensitivity to leptin, insulin, and melanocortin agonists. We postulated that such reduced sensitivities would be associated with decreased binding to the hypothalamic leptin, insulin, and melanocortin receptors in selectively bred DIO rats and in rats fed a high-energy (HE; 31% fat) diet for 7 wk. On HE diet, DIO rats gained 15% more weight and had 121% heavier fat pads and 70% higher leptin levels than low-fat chow-fed DIO rats. Diet-resistant (DR) rats gained no more weight on HE diet but had 68% heavier fat pads and 70% higher leptin levels than chow-fed DR rats. Compared with DR rats, DIO $^{125}$I-leptin binding was 41, 36, and 40% lower in the hypothalamic dorsomedial, arcuate, and dorsomedial portion of the ventromedial nuclei, respectively, and arcuate $^{125}$I-insulin binding was 31% lower independent of diet. In contrast,
Insulin in the Brain: There and Back Again

William A. Banks,1 Joshua B. Owen,2 and Michelle A Erickson3

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See other articles in PMC that cite the published article.

Abstract

Insulin performs unique functions within the CNS. Produced nearly exclusively by the pancreas, insulin crosses the blood-brain barrier (BBB) using a saturable transporter, affecting feeding and cognition through CNS mechanisms largely independent of glucose utilization. Whereas peripheral insulin acts primarily as a metabolic regulatory hormone, CNS insulin has an array of effects on brain that may more closely resemble the actions of the ancestral insulin molecule. Brain endothelial cells (BEC), the cells that form the vascular BBB and contain the transporter that translocates insulin from blood to brain, is itself regulated by insulin. The insulin transporter is altered by physiological and pathological factors including hyperglycemia and the diabetic state. The latter can lead
Leptin transport across the blood-brain barrier: implications for the cause and treatment of obesity.

Banks WA

Abstract
Leptin has emerged as a major regulator of adiposity. Leptin is released into the blood from fat cells and circulates to the brain where it crosses the blood-brain barrier (BBB) to act at receptors within the central nervous system to affect appetite, thermogenesis, and a number of other actions. In humans and in many rodent models, resistance to leptin appears to be a chief cause of obesity. Determining the cause of leptin resistance is fundamental to developing strategies for the use of leptin in obesity. The literature characterizing the transport of leptin across the BBB is reviewed. This literature strongly suggests that the cause of leptin resistance is due a decreased transport of leptin across the BBB in obese humans and rodents. The main cause of this resistance appears to be an impairment in the activity of the transporter rather than just simply saturation at higher doses. Strategies to overcome impaired BBB transport are reviewed, including the use of allosteric regulators and the delivery of material by the intrathecal route.
Marginal Contribution of POMC-LPRs to the Actions of Leptin in Insulin Deficiency

Fujikawa et al. 2013