Central Nervous System Control of Food Intake

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Introduction

Overview

- How leptin and insulin both influence energy homeostasis
- Specific pathways for both leptin and insulin
- Homeostasis is regulated both short term (a single meal) and long term (overall metabolic state)
What areas are we talking about in this paper?
Overview

Model for Energy Homeostasis
Adiposity Signals: Leptin and Insulin
Neuropeptide Effectors of Adiposity Signals
Neuropeptide Signaling Pathways in the Hypothalamus
Safety Signals Control Meal Size
Monoamine Neurotransmitters and Food Intake
Therapeutic Implications
2 Model Hypotheses

1) Short Term:
- Satiety signals from the gastrointestinal tract
- Inhibitory signals in proportion to body fat

2) Long Term:
- Inhibitory signals in proportion to body fat
Model for Energy Homeostasis

1. Leptin and insulin circulate in the blood in concentrations proportional to body fat content and energy balance.

2. Leptin and insulin act on central effector pathways in the hypothalamus, repressing brain anabolic neural circuits that stimulate eating and inhibit energy expenditure, while simultaneously activating catabolic circuits that inhibit food intake and increase energy expenditure.

3. Low leptin and insulin levels in the brain during weight loss increase activity of anabolic neural pathways that stimulate eating and suppress energy expenditure, and decrease activity of catabolic pathways that cause anorexia and weight loss.

4. Ingestion of food generates neural and hormonal satiety signals to the hindbrain. Leptin/insulin-sensitive central effector pathways interact with hindbrain satiety circuits to regulate the meal size, thereby modulating food intake and energy balance.

Food intake

Energy expenditure

- Metabolic rate
- Physical activity

Adiposity signals

Insulin/leptin

Fat stores

Energy balance

CNS

Anabolic

Catabolic
Signaling Pathways (Review)

**Insulin Receptor**
- Alpha subunits
- Beta subunits
- Tyrosine kinase domain
- Insulin-binding domain

**Tyrosine phosphorylation of intracellular signalling proteins**
- IRS-1
- tub

**Downstream signalling pathways**
- Activation of insulin-sensitive metabolic pathways and gene transcription

**Leptin Receptor**
- Leptin-binding domain

**JAK docking domain**
- Opens ATP-sensitive K⁺ channel
- Decreases neuronal firing rate

**Tyrosine phosphorylation of STAT proteins**
- Translocation to DNA in nucleus

**STAT activation**
- Activation of leptin-dependent gene transcription
Leptin and Insulin both meet the criteria for adiposity signal:

- Both hormones circulate at levels proportional to body fat content
- Both enter the CNS in proportion to their plasma level
- Receptors for both in brain neurons involved in energy intake
- Either peptide administered into the brain reduces food intake
Different mechanisms

- **Insulin**
  - As weight increases, insulin secretion increases in both basal state and in short term secretion

- **Leptin**
  - The rate of insulin-stimulated glucose utilization is a key factor relating leptin secretion to body fat mass
  - Leptin can be transiently dissociated from body fat because acute changes in energy can affect glucose metabolism

→ Leptin secretion depends on Insulin secretion
Leptin deficiency causes hyperphagia and obesity despite high insulin levels

**HYPERPHAGIA**
- **hyper**: excess
- **phagia**: chew

In contrast, insulin deficiency causes the inability to store body fat in adipocytes → Affects synthesis of leptin by altering homeostasis in adipocytes

In obese patients, the body creates a new basal level of leptin
Effect of leptin on hypothalamus and peripheral organs such as liver, pancreas, and smooth muscles. Leptin released from the adipocytes triggers the brain to regulate a host of responses, such as food intake, fertility, insulin secretion, and sympathetic tones, and exerts peripheral responses on the liver, pancreas, and the smooth muscles.
Diabetes Type 2

- Patients have both
  - Low leptin levels
  - Low insulin responsiveness
- If exogenously treat with leptin, diabetic hyperphagia was eradicated
- Implies that leptin may have crucial role in energy homeostasis
Leptin resistance and Obesity

- Elevated plasma leptin levels in obese humans, indicating resistance

Mechanisms:
- Decreasing ability of leptin to enter brain interstitial fluid
  - Impaired leptin transport across leptin endothelial cells
- Reduced leptin receptor signal transduction
  - Any damaged pathway component can cause leptin resistance
Neuropeptide Effectors

Arcuate Nucleus

NPY/AgRP neuron

NPY/AgRP expression

Food intake↑

Result

Para ventricular Nucleus

POMC neuron

α-MSH expression and release

Food intake↓
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Neuropeptide Signaling Pathways in the Hypothalamus
Decrease in Insulin/Leptin

- Fat cell mass
- [Leptin/insulin] expression
- [Leptin/insulin] action in hypothalamus

NPY/AgRP neuron
- Activates
- Inhibits

Arcuate nucleus
- ↑ NPY/AgRP expression
- ↑ NPY release
- ↑ AgRP release
- ↑ Food intake
- Paraventricular nucleus
- ↓ α-MSH expression and release
- Blocks binding of α-MSH to melanocortin receptors
- Activity of melanocortin anorexia pathways
- ↓ Food intake

POMC neuron
- Activates
- Inhibits

Paraventricular nucleus
- ↓ NPY release
- ↓ AgRP release
- ↓ Food intake

Increase in Insulin/Leptin

- Fat cell mass
- [Leptin/insulin] expression
- [Leptin/insulin] action in hypothalamus

NPY/AgRP neuron
- Inhibits
- Activates

Arcuate nucleus
- ↓ NPY/AgRP expression
- ↓ NPY release
- ↓ AgRP release
- ↓ α-MSH expression and release
- ↑ α-MSH binding and activation of melanocortin receptors
- ↑ Food intake

POMC neuron
- Activates
- Inhibits

Paraventricular nucleus
- ↑ AgRP inhibition of melanocortin pathways
- ↓ Food intake

Anorexia
- ↓ Food intake

Obesity
Both neurons in arcuate nucleus have insulin receptors and leptin receptors.

The arcuate nucleus is a major site for transducing afferent input from circulating leptin and insulin into a neuronal response.

Brain areas innervated by the arcuate nucleus are sites where second order energy homeostasis circuits are located.
PVN stimulation inhibits food intake
- Secretes 3 peptides: CRH (activates SNS, reg HPA)
  TRH (thyroid axis), Oxytocin (love hormone)

LHA stimulation excites food intake
- Secretes 1 orexigenic peptide -> MCH,
- Zona incerta and PFA
  (hypocretins -> increase in food and energy expenditure)
Mechanism for Satiety Information
- Afferent fibers of the vagus nerve and GI tract converge onto nucleus tractus solitarius (NTS) (in the brainstem)
- CCK is a humoral signal and converges onto NTS and suppresses food intake. Leptin potentiates CCK.
- Adiposity signals that reach the PVN and LHA also affects NTS
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5. Satiety Signals Control Meal Size
6. Monoamine Neurotransmitters and Food Intake
7. Therapeutic Implications
Where do they project?

- **Dopamine and Serotonin**
  - Functions:
    - Reward (motivation)
    - Pleasure, euphoria
    - Motor function (fine tuning)
    - Compulsion
    - Perseveration

- **Noradrenaline**
  - Functions:
    - Mood
    - Memory processing
    - Sleep
    - Cognition
Noradrenaline

- Db/db mice = resistant to leptin
- Fa/fa rats = mutant leptin receptors
- Ob/ob = leptin deficient

In some neurons (such as in the PVN), noradrenaline is co-localized with NPY

- Noradrenaline in PVN → Increases food intake → long term weight gain
- Ob/ob mice observe high levels of noradre.
Dopamine

- Motor impairments associated with dopamine deficiency that may also affect feeding behavior.
- Fasting and uncontrolled diabetes reduce synaptic dopamine reuptake (increasing synaptic dopamine levels)
- Mesolimbic pathway contributes to ‘reward’ aspect of consuming palatable food
Dopamine

- Dopamine in hypothalamus in dorsomedial and arcuate nuclei inhibits food intake
  - Ob/ob mice observe less dopamine in a.n.
  - Decreased hypothalamic dopamine contributes to hyperphagia induced by leptin deficiency
  - Leptin inhibits dopamine release from rat hypothalamus → How do we analyze this?
Serotonin

- Target for a lot of centrally acting drugs developed for obesity treatment (IE dexfenfluramine and sibutramine)
  - Drugs increase serotonin-receptor signalling and thereby suppress food intake
  - Antagonists have the opposite effect
    - 5HTKO $\rightarrow$ increase food intake and body weight
Serotonin

- Intact serotonin signaling is a component of normal energy homeostasis
- Leptin increases serotonin turnover → at least some of leptin's weight-reducing effects are mediated by increased serotonin signalling
- However, leptin-induced anorexia is intact even in 5HTKO, so it's only a component
If there are many different biological mechanisms for human obesity, perhaps we should understand and treat the specific mechanism affected in a particular patient.
Concept Questions

- POMC KO mice reversed obesity after treatment with MC4 receptor agonist
- Genetic leptin deficiency (ob/ob mice) reversed obesity by administering leptin
- Patients with leptin resistance will not respond to leptin unless resistance is overcome
- Patients with defective melanocortin receptor function won’t respond to leptin or MC4 agonist
“I’m a wife, a mother, a daughter, an executive, a cook, a housekeeper, a teacher, a chauffeur, and a soccer coach. That’s only 19 pounds per woman!”
“My doctor told me to locate the cause of my work-related stress and deal with it. Barnes, you’re fired.”
"My doctor told me to avoid any unnecessary stress, so I didn't open his bill."