Controlling Food Intake
Energy Homeostasis
(Change in body adiposity + compensatory changes in food intake)

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.
Background Information/Review

- Insulin secretion at pancreas
  - Glucose → GLUT2 → metabolism → ATP → Katp channel closes → depolarizes the cell → Ca2+ enters → triggers exocytosis of insulin

- Insulin effects muscle and fat
  - insulin → IR → PI3K → GLUT 4 synthesis → GLUT 4 transports to membranes → glucose enters cell → lowers blood glucose
Insulin Receptors

- 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

P
Insulin Receptor-Tyrosine Receptor

- located at hypothalamus, olfactory, hippocampus, cortex, and cerebellum
- MAPK path
  - Insulin $\rightarrow$ IR $\rightarrow$ **Tyrosine kinase** activates $\rightarrow$
    autophosphorylation $\rightarrow$ transphosphorylation $\rightarrow$ IRS1-4 $\rightarrow$
    Grb2 $\rightarrow$ SOS $\rightarrow$ Ras $\rightarrow$ Raf $\rightarrow$ MAP3K $\rightarrow$ MAP2K $\rightarrow$ **MAPK** $\rightarrow$
    gene expression and tau
- PI3K path
  - Insulin $\rightarrow$ IR $\rightarrow$ **TK** activates $\rightarrow$ autophosphorylation $\rightarrow$ PIP2 $\rightarrow$
    **PI3K** $\rightarrow$ PIP3 $\rightarrow$ (PDK1, Katp, Glu transport) $\rightarrow$ PKB/Akt $\rightarrow$
    (tau, mTOR, gene transcription, neuron survival)
Leptin Receptor

- Leptin binding domain
- Extracellular
- Intracellular
- JAK docking domain
- JAK
- Tyrosine phosphorylation of STAT proteins
- Translocation to DNA in nucleus
- Nucleus
- Activation of leptin-dependent gene transcription
- STAT
- P
- Decreases neuronal firing rate
- Opens ATP-sensitive K⁺ channel
- [K⁺]
- Glucose-responsive neurons
Leptin Receptor (cytokine receptor family)

- leptin $\rightarrow$ LepR $\rightarrow$ tyrosine phosphorylation $\rightarrow$
  - JAK $\rightarrow$ IRS $\rightarrow$ PI3K $\rightarrow$ PKB/Akt $\rightarrow$ neuron survival, tau (similar to insulin mech)
  - JAK $\rightarrow$ STAT $\rightarrow$ genes
  - JAK $\rightarrow$ opens Katp channel $\rightarrow$ more K+ exits $\rightarrow$
    hyperpolarizes cell $\rightarrow$ decreased firing rate $\rightarrow$
    inhibits food intake
ATP-Sensitive Potassium Channel

- Insulin closes Katp $\rightarrow$ depolarizes $\rightarrow$ faster firing rate
- Leptin opens Katp $\rightarrow$ hyperpolarizes $\rightarrow$ slower firing rate
Potential Mechanisms of Leptin Resistance

1) Impaired leptin transport across endothelial cells of the blood-brain barrier
   a) decreases the ability of circulating leptin to enter brain interstitial fluid to bind to neuronal leptin receptors

1) Reduced leptin-receptor signal transduction
   a) inhibition from protein ‘suppressor of cytokine signalling-3’ (SOCS-3)

1) Failure of neuronal effector pathway
   a) failure of one or more neuronal systems in the circuit to respond to the leptin signal
Effector Pathways

- **ANABOLIC**
  - Increases Food Intake & Decreases Energy expenditure
  - Arcuate Nucleus (first order neurons) signal Lateral Hypothalamus (second order neurons)
  - recall the ob/ob mice
    - no leptin → increased food intake → hyperphagia → obese

- **CATABOLIC**
  - Decreases food intake and increases energy expenditure
  - ARC and PVN
Anabolic Path

- decreased leptin → activate NPY/AgRP → inhibits POMC path → increases food intake → obesity
Catabolic Path

- increased leptin → activate POMC → inhibit NPY/AgRP → decrease food intake → anorexia
Leptin action in Hypothalamus

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<th>Activates</th>
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<td>Increase in Leptin</td>
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Neuropeptides

- **Orexigenic**
  - NPY/AgRP
  - MCH
  - Hypocretin 1, 2
  - galanin
  - noradrenaline

- **Anorexigenic**
  - α-MSH
  - CRH
  - TRH
  - CART
  - GLP1

- **anabolic**
  - increase food intake

- **catabolic**
  - decrease food intake
Neuropeptide Y (NPY)

- "the most potent orexigenic molecule"
  - but its effects are short-lived
- stimulates food intake and decreases energy expenditure
- repeated central administration leads readily to obesity
- secretion increased during active depletion of body fat stores and/or reduced leptin/insulin
- full response to leptin deficiency requires NPY signalling
Decreased Food Intake - Catabolic Pathway -
Anorexigenic Neuropeptides - Melanocortins

- Melanocortins suppress food intake!
  - they are “cleaved” from pro-opiomelanocortin (POMC) precursor molecule
  - promote negative energy balance
  - neuronal synthesis of these peptides increases in response to increased adiposity signalling in the brain
  - important role in energy homeostasis
Decreased Food Intake - Catabolic Pathway - Anorexigenic Neuropeptides - Melanocortins

- MC3 and MC4 Receptor Genes
  - melanocortin receptors
  - synthetic agonists of these suppress food intake (synthetic antagonists have opposite effect)
    - mice lacking MC4 are hyperphagic and obese
  - lack of full complement of central MC4 receptors predisposes to hyperphagia and pathological weight gain
    - findings extended to **humans**
Decreased Food Intake - Catabolic Pathway - Anorexigenic Neuropeptides - Melanocortins

- \( \alpha \)-melanocyte-stimulating hormone (\( \alpha \)-MSH)
- corticotropin-releasing hormone (CRH)
- thyrotropin-releasing hormone (TRH)
- cocaine-and amphetamine-regulated transcript (CART)
Model for Second-Order Neuronal Signalling Pathways

- Paraventricular Nucleus (PVN)
  - stimulation inhibits food intake -
    - bilateral lesions cause hyperphagic obesity syndrome
- Perifornical Area (PFA) and Lateral Hypothalamic Area (LHA)
  - stimulation activates food intake
    - bilateral lesions cause anorexia and weight loss
- Neuronal traffic flows bidirectionally between the ARC and these other hypothalamic sites
  - second-order neurons can actively modify the information that arrives there
- Leptin receptors on PVN and LHA neurons
Neuropeptides Synthesized in PVN

- Catabolic: reduce food intake/body weight when administered centrally
- CRH
  - causes anorexia
  - activates the sympathetic nervous system
  - major regulator of the hypothalamic pituitary adrenal axis
- TRH
  - reduces food intake
  - stimulates the thyroid axis
  - stimulates oxytocin (reduces food intake)
- prediction: they should be stimulated by melanocortin and/or CART signalling, but inhibited by NPY signalling
Neuropeptides Synthesized in LHA/PFA

- involved in anabolic signalling
- MCH
  - orexigenic peptide in LHA
  - synthesis is elevated by both energy restriction and leptin deficiency
    - MCH-knockout mice have reduced food intake and are excessively lean
  - G-protein-coupled receptor
- ‘Hypocretins 1 and 2’ or ‘Orexins A and B’
  - increase food intake
  - targeted deletion induces narcolepsy
- prediction: should be inhibited by melanocortin or CART input, and stimulated by NPY signalling
Transduction of Adiposity Signals Into a Neuronal Response

- the ARC is a major site for transducing afferent input from circulating leptin and insulin into a neuronal response
  - anorexic response to local microinjection of leptin into ARC
    - lesion of ARC leads to the inability of i.c.v. leptin to reduce food intake
- involuntary overfeeding of rats elicits a threefold increase in POMC
Adiposity Signals: Neuroanatomical Model

Adiposity signals

Fat mass

Satiety signals

Liver

Chemical

Energy metabolism

CCK release

Gl tract

Mechanical

Vagus nerve

Superior cervical ganglion

Cervical spine SNS afferents

NTS

Leptin

Insulin

POMC

NPY

ARC

PVN

PFA

LHA

Catabolic pathways

Response to satiety signals

Anabolic pathways
Circuit

- low adiposity signal → low leptin/insulin → activate anabolic (NPY) → inhibit catabolic (POMC) → increase food intake → increase in adiposity/leptin/insulin → activate CCK → activate NTS → Increase inhibition from vagus nerve → SATIETY
Controlling Satiety
Satiety

- **Satiety**
  - A biological state induced by neurohumoral stimuli generated during food ingestion that leads to meal termination

- **Satiety Factors**
  - Signals generated during a meal
  - Include peptides secreted from the gastrointestinal tract
  - Provide info to the brain that inhibits feeding and leads to meal termination
Adiposity Signals: Neuroanatomical Model

- Satiety information generated during the course of a meal is largely conveyed to the **hindbrain** by means of the afferent fibres of the **vagus nerve** and by afferents passing into the spinal cord from the upper gastrointestinal tract.
  - information converges at the nucleus tractus solitarius (NTS)

- The basic process of terminating a meal involves brain areas that can function in the absence of hypothalamic influences

- Leptin and insulin enhance the satiating effect of cholecystokinin (CCK)
Nucleus Tractus Solitarius (NTS)

- Hindbrain region that leads to the termination of individual meals
- Integrates sensory information from the gastrointestinal tract, abdominal viscera, and taste information from the oral cavity
  - Hypothesis: NTS neurons are responsible for integrating afferent info related to satiety with descending inputs from forebrain neurons involved in energy homeostasis
- Leptin potentiates the effect of CCK to activate NTS neurons
  - This demonstrates that the signals involved in energy homeostasis modulate the response of NTS neurons to input related to satiety

- Caveats:
  - NTS neurons have reciprocal interconnections with forebrain areas (PVN)
  - Hindbrain & forebrain may both process info involved in energy homeostasis
Noradrenaline or Norepinephrine

- increases food intake (inhibited by leptin)
- synthesized in dorsal vagal complex and locus ceruleus
  - these project caudally to the spinal cord and rostrally to the hypothalamus, thalamus, and cortex
- injection into the PVN increases food intake robustly
  - repeated injections result in weight gain
  - leptin may inhibit its release
  - acts like an anabolic effector in the CNS
- increased signaling in the PVN or other hypothalamic areas *may* contribute to hyperphagia induced by leptin deficiency
Monoamine Neurotransmitters and Food Intake

- decreases food intake but leptin effects uncertain
  - BUT food intake is critically dependent on its signalling
    - profound feeding deficits result from pharmacological depletion and genetic disruption of dopamine synthesis
- Complicated
  - deficiency also associated with motor impairments that may also affect feeding
  - feeding effects of dopamine vary with the brain region
Monoamine Neurotransmitters and Food Intake

Serotonin

- Decreases food intake
- The serotonin system
  - cell bodies in the caudal brainstem
  - projects from dorsal raphe nuclei
- primary target of several centrally acting drugs for obesity treatment
  - these drugs increase serotonin-receptor signalling and thereby suppress food intake
- 5HT-2C serotonin-receptor subtype
  - knockout of this receptor increases food intake and body weight
Therapeutic Implications

- Obesity resulting from reduced melanocortins
  - may respond to administration of melanocortin-receptor agonists
- Administering leptin to an obese human with genetic leptin deficiency
- The effects of AGRP on food intake in rodents warrant evaluation in the treatment of conditions associated with excessive weight loss (anorexia nervosa and wasting illness)
Conclusions

1) Food intake is highly regulated
   a) but it also has social factors

1) Satiety is highly biologically regulated
   a) meal size determined by onset of satiety

1) Obesity can arise from inherited or acquired defects in hormonal and/or neuropeptide signalling pathways
THANKS A BUNCH!