Central nervous system control of food intake

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Energy Homeostasis:

Initial model proposed by Kennedy in 1952

• Inhibitory signals proportional to body fat.
• Did not explain control of energy intake during individual meals.

Later Gibbs and Smith proposed satiety factors during meals.
Figure 1 Model showing how a change in body adiposity is coupled to compensatory changes of food intake. Leptin and insulin are adiposity signals, secreted in proportion to body fat content, which act in the hypothalamus to stimulate catabolic, while inhibiting anabolic, effector pathways. These pathways have opposing effects on energy balance (the difference between calories consumed and energy expended) that in turn determines the amount of body fuel stored as fat.
Adiposity Signals:

Insulin - Increase weight → increase insulin secretion

Failure of Beta cells to adapt → hyperglycemia (associates type 2 diabetes with obesity)

Leptin - autosomal recessive mutation of the gene encoding leptin → Rats became obese with hyperphagia.
Leptin secretion

Involves Flux through the hexosamine pathway

Acute changes in energy balance effect adipocyte glucose metabolism so leptin secretion can become transiently dissociated from levels of total body fat.

Compensatory response
Leptin secretion

Leptin has an important role in energy homeostasis.

Insulin is important for fat storage and leptin synthesis by fat cells (Example: uncontrolled diabetes mellitus)

Leptin may be more critical in energy homeostasis due to the fact that deficiency of leptin but not insulin leads to hyperphagia.
Insulin binding to the insulin receptor激活下游信号通路（PI3K, MAPK）

- Downstream signalling pathways (PI3K, MAPK)
  - Glucose Transport (GLUT4)
  - Glycogen synthesis
  - Cellular growth
  - Gene transcription
  - Protein synthesis
Leptin-Receptor Signaling

1. **Receptor**
   - On the cell surface
   - Binds to specific ligands (in this case Leptin)

2. **JAK**
   - Janus Kinase
     - Janus: Greek God of beginnings, gates, transitions
     - Kinase= enzyme that uses ATP to phosphorylate other proteins

2. **STAT**
   - Signal Transducer + Actuator of transcription
Leptin-Receptor Signaling
Leptin-Receptor Signaling

Leptin

JAK

STAT

P

ATP

Tyr

P

P

Tyr

P

P
Leptin-Receptor Signaling
Leptin-Receptor Signaling
Leptin Application → ‘glucose-responsive’ neurons become hyperpolarized (-firing)

- controls activity of ATP-sensitive K<sub>ATP</sub> channels
- closes K<sub>ATP</sub> channels
- increases intracellular K+
- depolarizes cell (+firing)

Leptin

- open configuration of K<sub>ATP</sub> channels
- K+ ions diffuse out of cell
- hyperpolarizes cell (-firing)
Leptin resistance and obesity

Leptin resistance can be caused by:

- Inability of leptin to cross BBB and enter CNS
- Mutated leptin receptor
- Reduced leptin signal transduction
- Increased SOCS-3 activity
Neuropeptide Y (NPY)

A signaling molecule that is found along anabolic effector pathways. Stimulates food intake and decreases energy expenditures.

Levels increase during the depletion of body fat stores and/or when there is reduced levels of leptin or insulin signaling in the brain.

A consequence of repeated NPY administration is obesity.

NPY administration also affects lipogenesis by triggering the release of lipogenic enzymes in the liver and white adipose tissue (WAT).
NPY and Lipogenesis

The process in which acetyl-CoA is converted into fatty acids. Through this process, overall energy can be stored in the form of fats.

An example of a lipogenic enzyme → acetyl-CoA carboxylase.

Acetyl-CoA \(\rightarrow\) (acetyl-CoA carboxylase) \(\rightarrow\) malonyl-CoA

Increased levels of malonyl-CoA \(\rightarrow\) increased food intake and decreased energy expenditure.

This relation reflects activity seen in the anabolic effector pathways.
NPY - Implications

*ob/ob* mice with the genetic knockout of NPY exhibit *reduces hyperphagia* and *obesity*.

**So what…?**

**Leptin**: NPY signaling is necessary in the face of deficient leptin levels.

**Insulin**: Insulin-deficient diabetes is accompanied by increased NPY synthesis.

**Lack of NPY** in mice: normal feeding responses found in the face of normal leptin/insulin levels and/or the genetic absence of NPY.

This suggests the presence **compensatory responses**.

AGRP, orexin, and certain melanocortins (MCH) are related.
Melanocortins

A family of signaling molecules that are usually found in catabolic effector pathways.

α-MSH, CRH, TRH, CART, and interleukin-1β are all peptides, cleaved from POMC, that induce a negative energy balance with all their respective syntheses occurring in response to increased adiposity signaling in the brain.
Melanocortins and Energy Homeostasis

**MC3r** and **MC4r** receptor activity → first evidence of melanocortins playing a role in energy homeostasis

- Synthetic agonist → suppression of food intake
- Synthetic antagonist → stimulates food intake

Mice lacking **MC4r** → **hyperphagic** and **very obese**

**MC3r** works as an inhibitor of the NPY/AgRP neuron

**MC4r** works as an inhibitor for secondary-downstream neurons
Agouti-related peptide (AgRP)

A signaling molecule found with NPY in the arcuate nucleus and along the anabolic effector pathway

**Stimulates** food intake and **decreases** energy expenditure

A consequence of AgRP administration is **hyperphagia**

**Antagonist** to MC3 and MC4 receptors → indicates importance regarding body weight regulation and overall energy homeostasis

Considered the most “robust” orexigenic signaling molecule
Neuropeptide signalling in the hypothalamus

- Historically, emphasis on “areas” that are inhibiting or increasing food intake

- Lesioning method was used. Spatial resolution not really good

Neuropeptide signalling in the hypothalamus

- **Lateral hypothalamic area (LHA)**: the “hunger area"
  - Contains the orexinergic nucleus
  - Functions: regulation of blood pressure, body temperature…

- **Ventromedial hypothalamic nucleus (VMN)**: the “satiety center”
  - Almost same functions as LHA, different location
Sagittal section of brain showing hypothalamic nuclei.

Key:
- Red: Mammillary region
- Blue: Tuberal region
- Green: Supraoptic region
- Purple: Preoptic region

Regions labeled:
- Intermediate mass of thalamus
- Dorsomedial nucleus
- Posterior hypothalamic nucleus
- Ventromedial nucleus
- Mammillary body
- Arcuate nucleus
- Infundibulum
- Pituitary gland
- Optic chiasm
- Corpus callosum
- Paraventricular nucleus
- Lateral preoptic nucleus
- Medial preoptic nucleus
- Anterior hypothalamic nucleus
- Suprachiasmatic nucleus
- Supraoptic nucleus
- Optic (II) nerve
Neuropeptide signalling in the hypothalamus

The “Upstream pathway”

- Transduction of adiposity into a neural signal
- Involve “first order neurons”
- Located in the arcuate nucleus in the mediobasal hypothalamus adjacent to third ventricule
The “upstream pathway”

- Can be divided into two subsets:

1) First-order neurons promoting food intake and reducing energy expenditure when activated.
   - NPY/AGRP (Agouti-related protein)
   - NPY and AGRP both have an anabolic effect - Increase food intake

2) First-order neurons reducing food intake
   - POMC/CART Pro-opiomelanocortin/Cocaine- and amphetamine-regulated transcript
   - Have a probolic effect - Decrease food intake
Experimental findings

- Overfed rats which produce leptin when body weight increase >5% of the total body mass. Quantity of POMC produced triples

- Injection of melanocortin-receptor antagonist increases food intake proving that CART have an anorexigenic effect
Third Ventricle

NPY/AGRP

POMC/CART

+++ ++++
The “downstream pathway”

- Play a role after transduction of signal

- Involves areas containing “second-order” neutrons connected to the “first-order ones” : Paraventricular nucleus (PVN), perifornical area (PFA) and Lateral hypothalamic area (LHA)

- PVN activation reduces food intake

- LHA is anabolic
Experimental results

- PVN stimulation → Food intake inhibition
- PVN lesioning → Hyperphagia
- LHA stimulation → Food intake stimulation
- LHA lesioning → Hypophagia

- Study of MCH within LHA
Interaction between Hypothalamic pathways and Satiety Signalling pathways

Lots of connection between hypothalamus and NTS

Insulin and leptin enhance satiating effect of CCK

   Explained by ability of central effector pathways to make NTS more sensitive to CCK

Signals involved in energy homeostasis directly modulate the response of NTS to satiety-related input
Interaction between long-term homeostatic signals and short-term satiety signals
Notes on the NTS

NTS integrates information from satiety signals with information about energy homeostasis

Integration of info involves many brain areas

Neuronal substrates involved in homeostasis pathways (MC4-receptor, Leptin receptors, POMC neurons) found in the NTS

NTS could be involved in energy homeostasis pathway by responding to leptin and project to areas in the hypothalamus
**Norepinephrine (NE)**

Synthesized in the *locus coeruleus* and *dorsal vagal complex* → projections span the entirety of brain

Co-localized with *NPY* in paraventricular nucleus of the hypothalamus (*PVN*)

Administration of *NE* → *PVN* increases food intake and can lead to *weight gain*

*Leptin* may inhibit *NE* release from terminals in brain area

Hypothesis: *Increased* *NE* signaling in *PVN* → *hyperphagia*, triggered by leptin deficiency

**Conclusion**: *NE* could possibly be an anabolic effector molecule
Dopamine (DA)

Synthesized in VTA/NaC/SN → projections span across numerous pathways

**Seems** to inhibit food intake (hypothalamus)

Depletion/disruption of DA synthesis results in feeding **deficits**

Feeding vs. Feeding behavior --> **Hypothalamic** vs. **Mesolimbic** pathways

**Decreased** hypothalamic DA → **hyperphagia** induced by leptin deficiency

**BUT:** Leptin **inhibits** DA release from hypothalamus → contradiction
Serotonin (5-HT)

Synthesized in **caudal brainstem**, including **dorsal raphe nuclei** → projections span across the entirety of the brain

System is targeted with regards to drugs that could treat **obesity**

- These drugs **increase** 5HT signaling, **reducing** food intake
- **5HT2c** receptor is involved in this process

Leptin’s effects on weight reduction can be mediated by the 5HT signaling, but it is **not required** (as seen in leptin-induced anorexic mice)
Energy homeostasis and meal size

Energy homeostasis pathways influence **meal size**

Centrally administered **NPY** causes overeating by larger meal sizes

**Leptin**-treated animals eat same number of meals as controls, but eat smaller meals.
Satiety signals control meal size

Meal size mostly determined by onset of **satiety** (fullness)

Satiety signals in the **NTS** (nucleus tractus solitarius) located in the brainstem

Meal termination induced by satiety signals still happens even when connections between hindbrain and forebrain are cut off

**NTS** integrates satiety input from gastrointestinal tract, liver, and gut hormones nerve and sympathetic fibers
Synaptic concentrations (e.g. DA)

Concentrations are determined by:

- **Rate of their release** from nerve terminals
- **Rate of their removal** from nerve terminals

**Transporter proteins** involved in mediation → expression influenced by **hormonal factors** (e.g. insulin)

Example: fasting and uncontrollable diabetes → **reduce** DA reuptake, and thus **increase** synaptic DA levels
Therapeutic implications

- Treatment with POMC
- Treatment with Leptin
- Leptin resistance seems more complicated to treat
- Not only treatment of diabetes but also help in the cure process of cancer or AIDS.