Appetite and satiety

- Alfred Fröhlich, 1901, Vienna
  - Dystrophia adiposogenitalis
    - Obesity, endocrine problems
  - Tumor of the hypothalamus
    - Arcuate nucleus

Heterington and Ranson, 1939: lesions in rats ‡ hyperphagia
Appetite and satiety

- **Midline Nuclei**
  1. Suprachiasmatic nucleus
  2. **Arcuate nucleus**
  3. Subfornical organ

- **Periventricular Zone**
  4. Periventricular nucleus
  5. **Paraventricular nucleus**

- **Medial Zone**
  5. Paraventricular nucleus
  6. Anterior hypothalamic nucleus
  7. Dorsomedial hypothalamic nucleus
  8. **Ventral lateral hypothalamic nucleus**
  9. Posterior hypothalamic nucleus
  10. Mammillary body
  11. Preoptic nucleus
  12. Supraoptic nucleus

- **Lateral Zone**
  11. Preoptic nucleus
  12. Supraoptic nucleus
  13. **Lateral hypothalamic nucleus**

*Nuclei that occupy more than one zone.*

*Figure 4-7 Hypothalamic zones and nuclei shown (A) in coronal view and (B) in longitudinal view. The plane of section in A is indicated by the vertical line in B.*
Appetite and satiety
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- Under conditions of stable body weight, there is a balance between food intake (energy in) and metabolism (energy out).
- Change in weight occurs when a shift from this balance occurs.
- For an individual there is an optimum weight as determined by a set point called the "lipostat."
- Because of this "lipostat" excessive eating or food deprivation often cause only temporary changes in weight.
- The early idea that body weight is regulated by a hypothalamic "center" involving a fasting center (Ventromedial nucleus, VMH) and an opposing feeding center (Lateral hypothalamus, LH) is now thought to be too simplistic.
Appetite and satiety: lipostat

- Experimental evidence
  - Animals defend against temporary weight losses and gains
  - Lipectomy effects are temporary
  - Lesioning the lateral hypothalamus lowers the set point
Appetite and satiety: short term

• Most large animals eat intermittently
  – Glycogen is an important buffer between meals
• Insulin lowers glucose levels following a meal
  – Promotes glucose uptake
  – Converts glucose to glycogen
  – Converts glucose to fatty acids
• Between meals, blood glucose falls causing secretion of another pancreatic hormone glucagon
  – Converts glycogen back to glucose
• The liver monitors glucose and fatty acid titers to elicit feeding behavior via the vagus nerve
Appetite and satiety: ghrelin

• Why we get hungry between meals?
  – Stomach distention, high glucose acts via the vagus
  – Intestinal release of CCK and PYY inhibits feeding
  – Ghrelin decreases immediately after a meal

• Why do we feel sated after a meal?
  – Blood concentrations of ghrelin are lowest shortly after consumption of a meal, then rise during the fast just prior to the next meal.
Long term regulation of food ingestion involves neuropeptides which stimulate or inhibit feeding

- Lateral hypothalamus and other nuclei are important in feeding behavior
  - LH secretes Orexin and Melanin concentrating hormone (MCH)
  - Neuropeptide Y (NPY) and Agouti related peptide (AgRP) stimulates feeding
    - Both act at PVN and LH
      - Stimulates release of orexin and MCH
  - CART and α-MSH inhibit feeding
    - High Leptin initiates secretion of these neuropeptides

- Leptin is secreted by well-nourished fat cells
  - Leptin acts on the neuropeptides pathways of the hypothalamus
  - Leptin also influences reproduction and insulin levels
Appetite and satiety

- Leptin from fat tissue
- Insulin from pancreas
- Ghrelin from stomach
- GLP1/PYY from intestine
- NPY
- AGRP
- α-MSH
- CART
- PVN
- VMH
- LHA
- MC4

Effector systems

- Food intake
- Energy expenditure (TRH etc.)

Peripheral organs

- Hypothalamus

First order neurons

- FASTEN
- catabolic anorexigenic
- anabolic orexigenic

Second order neurons

- NTS
- Satiation

Arcuate nucleus

- Orexin
- LHA
- MCH +

Vagus afferences

- Leptin
- Insulin
- Ghrelin
- GLP1/PYY

EAT

anabolic
orexigenic

FASTEN

catabolic
anorexigenic
Appetite and satiety

Produced by adipose (fat) tissue, leptin suppresses appetite as its level increases. When body fat decreases, leptin levels fall, and appetite increases.

Secreted by the stomach wall, ghrelin is one of the signals that triggers feelings of hunger as mealtimes approach. In dieters who lose weight, ghrelin levels increase, which may be one reason it's so hard to stay on a diet.

A rise in blood sugar level after a meal stimulates the pancreas to secrete insulin (see Figure 41.3). In addition to its other functions, insulin suppresses appetite by acting on the brain.

The hormone PYY, secreted by the small intestine after meals, acts as an appetite suppressant that counters the appetite stimulant ghrelin.
The effects of leptin were observed by studying mutant obese mice (ob/ob) that arose at random within a mouse colony at the Jackson Laboratory in 1950. These mice were massively voracious. Leptin itself was discovered in 1994 by Jeffrey M. Friedman and colleagues at the Rockefeller University through the study of such mice.

- Leptin circulates at levels proportional to body fat
- Enters the CNS in proportion to its plasma concentration
- Its receptors are found in brain neurons involved in regulating energy intake and expenditure

Appetite and satiety: leptin
Appetite and satiety: leptin

- Leptin enters at the median eminence (circumventricular organ) and binds to receptors in the arcuate nucleus
  - Leptin receptor belongs to the cytokine family SOCS3
- Leptin acts by activating neurons expressing α-MSH and CART and inhibiting neurons containing neuropeptide Y and agouti-related protein (AgRP)
  - α-MSH suppress feeding, AgRP increases feeding
- Both project to overlapping fields of the paraventricular nucleus and lateral hypothalamus and have antagonistic effects
Appetite and satiety: melanocortin

Intermingling of neurons that stain with a digoxygenin-labeled probe for MCH mRNA (blue) and with antiserum against ORX (brown)

Virtually no colocalization within individual neurons

Close relationship of axons that stain immunohistochemically for agouti-related protein (AgRP, panels B, E), α-melanocyte-stimulating hormone (α-MSH, panels C, F), or neuropeptide Y (NPY, panels D, G), with cell bodies in human brains that are immunoreactive for MCH (B–D) and ORX (E–G)
Appetite and satiety

Leptin
Fat tissue
Insulin
Pancreas
Ghrelin
Stomach
GLP1/PYY
Intestine
NPY
AGRP
α-MSH
CART
PVN
VMH
LHA
MCH + Orexin
Nucleus of the solitary tract (NTS)
Paraventricular nucleus (PVN)
Lateral hypothalamic area (LHA)
Eating center (EAT)
Average satiation (MCH + Orexin)
Agouti-related peptide (AGRP)
Neuropeptide Y (NPY)
Metacortex-4 (MC4)
MC4 receptor-KO (cancer cachexia)
Mice overexpressing AgRP are obese
Injection of NPY and AgRP increase feeding
MCH-KO-mice are hypophagia and lean
Food intake
Food intake
KO for MC4-receptor (Obese)

Effector systems
Peripheral organs
Hypothalamus

Injection of NPY and AgRP increase feeding
KO for MC4-receptor
Obese (cancer cachexia)

Absence of leptin lead to hyperphagia
Leptin receptor mutation db/db lead to obesity

Food intake
Energy expenditure
Fat and glucose metabolism

Vagus afferences
1st order neurons
d2nd order neurons

Food intake
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The melanin concentrating hormone and orexin neurons in the human lateral hypothalamus

Clusters of neurons containing each peptide are interlaced with clusters containing the other peptide