Feeding Behavior 2

- Endocrine and neural mechanisms

Leptin

- For long-term regulation of feeding behavior
- Fat cells (adipocytes) secrete leptin (peptide hormone)
- Leptin receptors in brain (hypothalamus)
- Low levels of leptin *signaling* increase hunger and decrease physical activity and immune activity
- High levels of leptin *signaling* decrease hunger and increase physical activity and immune activity
Positional cloning of the mouse obese gene and its human homologue

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The mechanisms that balance food intake and energy expenditure determine who will be obese and who will be lean. One of the molecules that regulates energy balance in the mouse is the obese (ob) gene. Mutation of ob results in profound obesity and type II diabetes as part of a syndrome that resembles morbid obesity in humans. The ob gene product may function as part of a signalling pathway from adipose tissue that acts to regulate the size of the body fat depot.

Mouse on left cannot produce leptin. Injections of leptin are effective. The “obesity gene” ??

FIG. 2. Tissue distribution of the 2G7 transcript. a, Northern blot of total RNA (10 µg) from various tissues probed with labelled 2G7 exon. The 2G7 exon was identified using exon trapping with DNA from a pool of P1 clones in the region of ob. This probe hybridized specifically to RNA from white adipose tissue. Autoradiograph signals appeared after 1-h exposure (24-h exposure shown here). The transcript migrated between 28S and 18S ribosomal RNA markers and is estimated to be ~4.5 kb.
Leptin

• Giving obese people injections of leptin does not strongly decrease hunger and reduce weight
• Most obese people are less sensitive to leptin
• Exercise increases sensitivity to leptin…
• Insulin blocks leptin signaling…
  – What could be an evolutionary explanation?
• Leptin sensitivity naturally declines during pregnancy and when animals prepare for hibernation
Arcuate Nucleus

• In hypothalamus
• Integrates information from various parts of the body regarding energy stores
• Projects to other areas of hypothalamus to regulate feeding (circuit, many signaling molecules)
• 2 kinds of neurons in arcuate nucleus
  – “hunger motive” neurons increase feeding
  – “satiety motive” neurons decrease feeding
Neural Regulation of Feeding

Two kinds of neurons in the arcuate nucleus of the hypothalamus

Ghrelin (hunger signal)
Taste input
Leptin (long-term satiety signal)
Insulin (intermediate-term satiety signal)
CCK (short-term satiety signal)

Hunger-motive

NPY, AgRP, & GABA

Two kinds of neurons in the lateral nucleus of the hypothalamus

Ghrelin (increases arousal)

Orexin/hypocretin (increases arousal)

Two kinds of neurons in the paraventricular nucleus of the hypothalamus

Neurons in the paraventricular nucleus of the hypothalamus

Response to highly palatable foods

Amygdala and related areas

Suppressed eating during illness; avoidance of foods previously associated with illness

Output to other areas, including cerebral cortex and brainstem. Output increases feeding.
Paraventricular Nucleus (PVN)

- Both kinds of neurons in arcuate nucleus project to paraventricular nucleus of hypothalamus (PVN)
- PVN inhibits the lateral hypothalamus (LH), an area important for increasing feeding
- For example: Satiety-motive neurons of the arcuate nucleus (via melanocortins) stimulate the PVN…and thus inhibit the LH…and thus decrease feeding
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Paraventricular Nucleus (PVN)

- Electrical or chemical (excitotoxic) lesions of PVN cause overeating
  - Disinhibition of LH
  - Eat larger meals but not more frequent meals
- These data suggest that the PVN is important for satiety
  - PVN lesions cause insensitivity to signals that end meals
Chemical Inhibition the PVN in Rats
Neural Regulation of Feeding

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- Leptin (long-term satiety signal)
- Insulin (intermediate-term satiety signal)
- CCK (short-term satiety signal)
- Taste input
- NPY, AgRP, & GABA
- Two kinds of neurons in the arcuate nucleus of the hypothalamus

**Hunger-motive**

- Ghrelin
- Orexin/hypocretin (increases arousal)
- Output to other areas, including cerebral cortex and brainstem. Output increases feeding.

**Satiet-y-motive**

- Melanocortin
- Neurons in the paraventricular nucleus of the hypothalamus
- Response to highly palatable foods
- Suppressed eating during illness; avoidance of foods previously associated with illness
- Amygdala and related areas
Lateral Hypothalamus (LH)

- Bilateral mild electrical stimulation of LH
- Bilateral electrical lesions to LH

Stage 1. Aphasia and adipsia. Rat refuses all food and drink; must be force-fed to keep it alive.

Stage 2. Anorexia. Rat eats a small amount of palatable foods and drinks sweetened water. It still does not eat enough to stay alive.

Stage 3. Adipsia. The rat eats enough to stay alive, though at a lower-than-normal body weight. It still refuses plain water.

Stage 4. Near-recovery. The rat eats enough to stay alive, though at a lower-than-normal body weight. It drinks plain water, but only at meal-times to wash down its food. Under slightly stressful conditions, such as in a cold room, the rat will return to an earlier stage of refusing food and water.
LH and axons

• BUT: many axons of dopaminergic neurons pass through the LH
• Electrical lesions destroy these axons, as well as the cell bodies in the LH
• How to lesion cell bodies in the LH but not axons passing through?
LH and insulin

- LH also regulates insulin secretion
  - How might this be related to feeding?
  - How could the LH regulate insulin secretion?
  - Effect of LH lesions on circulating insulin levels?
Orexin

• LH neurons release orexin (hypocretin)
• Orexin increases arousal and motivation to seek food
  – Influences response to incentives and reinforcement in general
Neural Regulation of Feeding

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- Neurons in the paraventricular nucleus of the hypothalamus
- Neurons in the lateral nucleus of the hypothalamus
- Orexin/hypocretin (increases arousal)
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Pathways From LH

- Nucleus accumbens (control of ingestion and swallowing)
- Thalamus
- Somatosensory cortex (taste perception)
- Prefrontal cortex (food-seeking behaviors)
- Hypothalamus
- Nucleus of the tractus solitarius (NTS)
Ventromedial hypothalamus (VMH)
Ventromedial Hypothalamus (VMH)

- Interconnected with multiple hypothalamic areas
- Output from the ventromedial hypothalamus (VMH) decreases feeding
- VMH electrical lesions: greatly increase feeding
  - increase in fat stores and body weight
  - rats eat normal-sized meals but more frequently
Effects of VMH lesions

(a) Two rats. (b) Graph showing body weight and food intake over time after VMH lesions.
VMH and insulin

- VMH decreases insulin secretion
- VMH lesions increase insulin secretion
  - animals store too much of food eaten as fat
- if food intake is limited to normal levels (matched to controls), the VMH-lesioned rats still have higher fat and body weight than controls!
- VMH-lesioned rats overeat because they are storing too much of food eaten as fat; they are not fat simply because they overeat
- In VMH-lesioned rats, fat stores are huge, but other cells are “semi-starving”