Wired to Eat: Brain Pathways and the Foods We Eat

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Weight Regulation Questions

What governs how much we eat?

Why do we have cravings?
Mapping the Brain Circuitry

The Hypothalamus

The Brainstem
Alexis Shapiro (nbcnews.com)

Craniopharyngioma Surgery Causes “Hypothalamic Obesity”

“She’s always hungry,” [her mother] said. “... we’ve had to padlock the cupboard.”
Brainstem Cavernoma
“Brainstem Obesity”

Hypothalamus

Oculomotor cortex
(includes Eddinger–Westphal nucleus)

Dorsal motor nucleus of the vagus

Nucleus ambiguus

LPBN

Satiety Center

VNAB

To spinal cord

Medial forebrain bundle
Dorsal longitudinal fasciculus
Hypothalamic control of energy homeostasis by adiposity signals: The Set Point

- Decrease body fat:
  - Food Intake ↓
  - Energy Expenditure ↑

- Increase body fat:
  - Food Intake ↑
  - Energy Expenditure ↓

**NPY/AgRP**

**Arcuate**

**LEPTIN**

**INSULIN**

**PVN**

**LHA**

**MC4R**

**POMC → α-MSH**

**CART**

**NPY**

**AgRP**

**Orexins**

**MCH**

**Set Point**

**Set Point**

**Set Point**
The body weight SET POINT is tightly regulated to limit weight loss (or gain) and restore baseline weight following caloric restriction (overfeeding).
How does the SET POINT know how much you weigh?
Leptin

Effect of Leptin Treatment in Children with Leptin Deficiency

How does the SET POINT know how much you eat?
Body Weight Set Point is Receives Signals from Gut Hormones During Meal

Ghrelin $\rightarrow$ ↓ hunger

- PYY
- insulin/amylin
- GLP-1
- CCK
$\rightarrow$ ↑ satiety

How does what you eat influence the SET POINT?
Effect of a High-Fat Diet on Feedback Signals from Adipose Tissue and the Gut

- Weak or impaired signaling by leptin and GLP-1
- Weak (or no) ↓ Ghrelin
- Weak or impaired ↑ insulin, GLP-1

Two-week overt manipulation of the fat content of the diet in healthy women: Increased Food Intake

Energy intake

<table>
<thead>
<tr>
<th>Dietary fat intake (%)</th>
<th>Energy intake (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-20</td>
<td>1750</td>
</tr>
<tr>
<td>30-35</td>
<td>2250</td>
</tr>
<tr>
<td>45-50</td>
<td>2750</td>
</tr>
</tbody>
</table>

* 30% increase

Effects of a Protein and Complex Carbohydrates on Feedback Signals from Adipose Tissue and the Gut

What about sugar?

Sugar = glucose + fructose

Relative sweetness of sugars and sweeteners:

- Lactose: 16
- Galactose: 32.1
- Maltose: 32.5
- Invert sugar: 50
- Glucose: 74.3
- Honey: 97
- HFCS-42%: 100
- Sucrose: 100
- Fructose: 173

Nearly 3x sweeter
Temporal response of the Glucose after eating revealed by functional MRI

Differential Effects of Fructose vs Glucose on Hypothalamic Signaling

US (world!) Populations: Increased Dietary Intake of Sugar-Added Foods
What most people call “sweets” are actually combinations of fat and simple sugar (fructose).
The “holy grail” for increasing calorie intake: Fat + Sugar + make it liquid
Maximizing Our “Obesogenic” Environment
Reward Control of Food Intake and In Addiction
Food Intake ≠ Addiction


- Nearly 9x greater effect
- Neuroadaptations require greater amounts with subsequent exposures.
- Does not extinguish.
Body Weight Set Point: Complex Signaling Systems Govern How Much We Eat

Impulse Control: Want vs. Don’t Want

Reward pathways: Like vs. Don’t Like
- GI system
  - GLP-1
  - PYY
  - CCK
  - Insulin/amylin
  - Ghrelin
- Adipose tissue
  - Leptin

Why do we have cravings?
Weight Regulation Questions

I have no idea...

But that’s what makes science cool.
Brain Activation to Pictures of High and Low-Calorie Foods
Brain Representation of Odors
Brain Activation to Taste
Obesity results when leptin resistance (deficiency) occurs, establishing a higher body weight SET POINT.