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Overall Control of Appetite

- Brain centers
- Neuropeptides
- Insulin
- Adipose hormones
- Other hormones
Brain Centers That Control Appetite

- Hypothalamus
- Brainstem
- Nucleus accumbens
- Ventral pallidum
- Mesolimbic dopamine system (VTA NAc)
- Other reward centers

Neuropeptide Control of Appetite

Neuropeptides regulate energy homeostasis.

- Neuropeptide Y
- Leptin
- Orexin-A (hypocretin-1)
- Orexin-B (hypocretin-2)
Hormonal Control of Appetite

- Insulin
- Glucagon
- Leptin
- Ghrelin
- Other hormones synthesized by adipose tissue
- Gut hormones

These reflect the long-term nutritional status of the body and are able to influence neural circuits.

Appetite Hormones

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Appetite Related Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylin</td>
<td>• Delays gastric emptying</td>
</tr>
<tr>
<td></td>
<td>• Lowers blood glucose</td>
</tr>
<tr>
<td>CCK (cholecystokinin)</td>
<td>• Suppresses hunger and signals satiety</td>
</tr>
<tr>
<td></td>
<td>• Inhibits gastric emptying</td>
</tr>
<tr>
<td></td>
<td>• Stimulated gallbladder secretion</td>
</tr>
<tr>
<td></td>
<td>• Influences PYY release</td>
</tr>
<tr>
<td></td>
<td>• Stimulated by fat and protein</td>
</tr>
<tr>
<td>CRF (corticotropin-releasing factor)</td>
<td>• Reduces appetite</td>
</tr>
<tr>
<td>Dopamine</td>
<td>• Reinforces pleasure from food</td>
</tr>
<tr>
<td></td>
<td>• Contributes to cravings</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>• Triggers hunger</td>
</tr>
<tr>
<td></td>
<td>• Increases preference for fatty and sweet foods</td>
</tr>
<tr>
<td></td>
<td>• Increases gastric motility</td>
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</tbody>
</table>
### Appetite Hormones

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<tr>
<td>GIP (glucose-dependent insulinotropic polypeptide)</td>
<td>• Stimulates insulin release while eating; diabetics become resistant to GIP</td>
</tr>
</tbody>
</table>
| GLP-1 (glucagon like peptide 1)     | • Slows gastric emptying  
      • Promoted insulin release and inhibits glucagon  
      • Suppresses appetite |
| Glucagon                        | • Increases satiety                                                                        |
| Insulin                         | • Lowers blood glucose  
      • Stimulated glycogen synthesis  
      • Stimulates fat synthesis and storage                                                  |
| Leptin                          | • Decreases food intake  
      • Regulates metabolism                                                                |
| Adiponectin                     | • Enhances fatty acid oxidation and reduces triglycerides  
      • Stimulates glucose uptake by muscle  
      • Inhibits glucose production by the liver  
      • Decreases blood glucose levels  
      • Decreases appetite                                                                   |
| NPY (neuropeptide Y)            | • Stimulates appetite                                                                      |
| OXM (oxyntomodulin)             | • Inhibits ghrelin secretion  
      • Suppresses appetite  
      • Slows gastric emptying  
      • Stimulates insulin release after carbohydrate intake                                  |
| PP (pancreatic polypeptide)      | • Slows gastric emptying                                                                   |
| PYY (peptide YY)                | • Slows gastric emptying  
      • Suppresses appetite  
      • Stimulates satiety (levels are highest 90 minutes after starting a meal)             |
| Serotonin                       | • Decrease linked with carbohydrate cravings  
      • Provides calm feeling after eating sugar                                                |
| Orexin                          | • Promotes eating beyond satiety                                                           |
| Melatonin                       | • Sleep deprivation decreases melatonin production, which decreases leptin and increases ghrelin production |
| Sex hormones                    | • Estrogen suppresses appetite  
      • Imbalance estrogen/progesterone ratio can trigger intense food cravings               |
| Cortisol                        | • Sustained high levels can lead to intense cravings and binge eating                      |
Leptin

- Secreted by the fat cells – the white adipose tissue
- Signals the hypothalamus and pancreas “we are full”
- Hypothalamus response is to turn off appetite
- Pancreas response is to stop producing insulin
- Has a 24-hour circadian rhythm and is controlled by eating
- Pancreas and hypothalamus become leptin resistant

Normal Leptin Function

Chart from: Richards BJ. Mastering Leptin. Minneapolis: Wellness Resources Books, 2004
INÉ: Digestion - Endocrinology of Appetite

Leptin Resistance

Leptin levels peak two hours after a meal and then decline. Over time, leptin resistance occurs as the level of leptin decreases and the body becomes more insulin resistant. Insulin resistance can be reversed with diet and exercise.

**Chart from:** Richards BJ. Mastering Leptin. Minneapolis: Wellness Resources Books, 2004

Things That Disrupt Leptin Signaling

- High carbohydrate meal in the morning
- Eating too frequently
- Insufficient sleep
- Insulin resistance
- Fungicide tolyfluanid and other endocrine disruptors
- Bisphenol A (BPA)

Leptin Modulation

**Increase:**
- Insulin
- Cortisone
- Estrogens

**Decrease:**
- Adrenaline
- Male hormones
- Growth hormone

http://www.DrRitamarie.com
Optimizing Leptin and Insulin
- Avoid eating after dinner
- Stick to three meals a day; no snacking
- Allow five to six hours between meals
- Avoid large meals
- Eat slowly
- Eat a breakfast containing protein
- Reduce intake of starchy carbohydrates

Meal Timing and Leptin
- Avoid snacking: Prolonged insulin curves or more frequent insulin spikes plus decreased leptin promote obesity
- Maintain ideal body weight: Obesity increases insulin resistance
- Avoid eating at night: Late eating increases insulin and decreases growth hormone and leptin
- Avoid high-carbohydrate breakfasts: Morning carb overdoes cause a premature spike in leptin and food cravings
- Eat protein within an hour of waking: Morning protein consumption promotes growth hormone and regulates insulin

Ghrelin
- Secreted by cells in the stomach wall
- Eating suppresses ghrelin
- An empty stomach secretes ghrelin freely
- Ghrelin stimulates appetite
- Ghrelin is a potent stimulator of growth hormone
- Waiting to eat until very hungry and stomach is empty stimulates fat burning and muscle sparing
Resistin
- Peptide secreted by fat cells
- Discovered in 1995
- Named for ability to resist insulin
- Links obesity, insulin resistance, and diabetes
- AKA adipose tissue-specific secretory factor (ADSF)
- Cysteine-rich adipose-derived peptide hormone encoded by the RETN gene
- Increases insulin resistance as more fat cells accumulate around the waist
- These fat cells secrete leptin

Orexin
- A neuropeptide released by the posterior lateral hypothalamus
- Linked to wakefulness and sleep, appetite regulation, and the motivation of sexual and addictive behaviors
- Often described as “a hormone in the brain with the effects of adrenaline and testosterone in one”
- Plays a key role in promoting eating and appetite and seems to work to signal “eat more,” beyond satiety
- Two variations identified

Neuropeptide Y (NPY)
- Most abundant neuropeptide in the brain
- Possibly stronger than ghrelin at stimulating appetite
- Rats given an NPY will crave sugar water over sex
- The primary trigger is calorie restriction and low leptin
- Primary job is to delay the feeling of fullness
- Tells the body where and how to store extra calories as either fat or muscle
- High levels will cause less fullness and calories will preferentially be stored as fat
Neuropeptide Y (NPY) Interactions
- Leptin inhibits NPY
- Hypothalamic NPY stimulates the secretion of insulin and cortisol and shifts metabolism to favor synthesis and storage of fat
- Weight loss caused by caloric restriction ("dieting") stimulates NPY release in the periventricular nucleus

Adiponectin
- 244-amino-acid-long polypeptide
- Produced by adipose tissue
- Increases metabolic rate
- Plays an important role in the energetic capacity of skeletal muscle
- Counteracts inflammation and insulin resistance
- Important for weight loss
- Increases insulin sensitivity and affects insulin levels
- A deficiency makes it almost impossible to melt fat and stay thin - helps the body use fat to fuel muscle cells

Adiponectin Causes Weight Loss Without Affecting Appetite
- Receptors in the hypothalamus and some forms enter the cerebrospinal fluid
- Enhances fatty acid oxidation in muscle and liver, thus reduces triglyceride content in these tissues
- Stimulates glucose uptake by skeletal and cardiac muscle and inhibits glucose production by the liver
- Decreases blood glucose levels
- Needed to turn fat into energy - helps the body use fat to fuel muscle cells
Food and Adiponectin

- Daily intake of fish or omega-3 supplementation increased adiponectin levels by 14-60%.
- Weight loss with low-calorie diet plus exercise increased adiponectin levels in the range of 18-48%.
- A 60-115% increase in adiponectin levels with fiber supplementation.
- High-carbohydrate meals associated with lower adiponectin.
- Extracts of sweet potatoes have been reported to increase levels.

Diet and Adiponectin

- Magnesium associated with higher adiponectin.
- Coffee associated with high adiponectin and low leptin.
- Moderate alcohol intake is associated with higher adiponectin concentrations.
- Intermittent fasting can increase adiponectin levels.
- Sleep can increase adiponectin levels.
- Ayurvedic combination:
  - Betel - Piper betle
  - Dolichos biflorus
Adiponectin and Inflammation

- **Study In Mice:**
  - Mice given TNF-alpha, which caused the release of inflammatory cytokines
  - Injecting with adiponectin reversed the effects of the cytokines and inflammation

Effects of Adiponectin

- Decreases gluconeogenesis
- Increases glucose uptake
- Increases β-oxidation
- Increases triglyceride clearance
- Protection from endothelial dysfunction
- Improves insulin sensitivity
- Promotes weight loss
- Controls energy metabolism
- Reduces TNF alpha

Adiponectin Connections

- Lower levels associated with ADHD in adults
- Increased in rheumatoid arthritis
- Exercise-induced release of adiponectin increased hippocampal growth and led to antidepressive symptoms in mice
Adiponectin and Fats

- 10 week study with 17 healthy subjects
  - Increased omega-3 intake and decreased omega-6 intake
  - Result: Significant reductions in TNF-alpha and low-density lipoprotein-cholesterol along with increased adiponectin

Adiponectin as a marker for metabolic syndrome

- Increased omega-3 intake and decreased omega-6 intake
- Result: Significant reductions in TNF-alpha and low-density lipoprotein-cholesterol along with increased adiponectin concentration and fatty acid oxidation in healthy subjects. Eur J Nutrition. 2007

Resources and References

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