Digestion: Endocrinology of Appetite

Dr. Ritamarie Loscalzo
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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)
FIGURE 1 Stimulatory peptides (placed around the >0 sign; left part of the figure) and inhibitory peptides (placed around the <0 sign; right part of the figure) involved in food intake regulation. AgRP: agouti-related peptide; CART: cocaine- and amphetamine-related peptide; GHRH: growth hormone-releasing hormone; MCH: melanin-concentrating hormone; TRH: thyrotropin-releasing hormone; α-MSH: alpha-melanocyte-stimulating hormone; CNTF: ciliary neurotrophic factor; BDNF: brain-derived neurotrophic factor; CGRP: calcitonin gene-related peptide; PACAP: pituitary adenylate cyclase-activated peptide; GLP: glucagon-like peptide; NT: neurtensin; TNFα: tumor necrosis factor alpha; Apo AIV: apolipoprotein AIV; CRH: corticotropin-releasing hormone; CCK: cholecystokinin.
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>
</table>
| Amylin                            | • Delays gastric emptying  
• Lowers blood glucose                                                                   |
| CCK (cholecystokinin)             | • Suppresses hunger and signals satiety  
• Inhibits gastric emptying  
• Stimulated gallbladder secretion  
• Influences PYY release  
• Stimulated by fat and protein |
| CRF (corticotropin-releasing factor)| • Reduces appetite                                                                          |
| Dopamine                          | • Reinforces pleasure from food  
• Contributes to cravings                                                                  |
| Ghrelin                           | • Triggers hunger  
• Increases preference for fatty and sweet foods  
• Increases gastric motility                                                             |
# Appetite Hormones

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<thead>
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<tbody>
<tr>
<td>GIP (glucose-dependent insulinotropic polypeptide)</td>
<td>• Stimulates insulin release while eating; diabetics become resistant to GIP</td>
</tr>
<tr>
<td>GLP-1 (glucagon like peptide 1)</td>
<td>• Slows gastric emptying&lt;br&gt;• Promoted insulin release and inhibits glucagon&lt;br&gt;• Suppresses appetite</td>
</tr>
<tr>
<td>Glucagon</td>
<td>• Increases satiety</td>
</tr>
<tr>
<td>Insulin</td>
<td>• Lowers blood glucose&lt;br&gt;• Stimulated glycogen synthesis&lt;br&gt;• Stimulates fat synthesis and storage</td>
</tr>
<tr>
<td>Leptin</td>
<td>• Decreases food intake&lt;br&gt;• Regulates metabolism</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>• Enhances fatty acid oxidation and reduces triglycerides&lt;br&gt;• Stimulates glucose uptake by muscle&lt;br&gt;• Inhibits glucose production by the liver&lt;br&gt;• Decreases blood glucose levels&lt;br&gt;• Decreases appetite</td>
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<tr>
<td>NPY (neuropeptide Y)</td>
<td>• Stimulates appetite</td>
</tr>
<tr>
<td>OXM (oxyntomodulin)</td>
<td>• Inhibits ghrelin secretion</td>
</tr>
<tr>
<td></td>
<td>• Suppresses appetite</td>
</tr>
<tr>
<td></td>
<td>• Slows gastric emptying</td>
</tr>
<tr>
<td></td>
<td>• Stimulates insulin release after carbohydrate intake</td>
</tr>
<tr>
<td>PP (pancreatic polypeptide)</td>
<td>• Slows gastric emptying</td>
</tr>
<tr>
<td>PYY (peptide YY)</td>
<td>• Slows gastric emptying</td>
</tr>
<tr>
<td></td>
<td>• Suppresses appetite</td>
</tr>
<tr>
<td></td>
<td>• Stimulates satiety (levels are highest 90 minutes after starting a meal)</td>
</tr>
<tr>
<td>Serotonin</td>
<td>• Decrease linked with carbohydrate cravings</td>
</tr>
<tr>
<td></td>
<td>• Provides calm feeling after eating sugar</td>
</tr>
<tr>
<td>Orexin</td>
<td>• Promotes eating beyond satiety</td>
</tr>
</tbody>
</table>
# Other Hormones that Influence Appetite

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<tr>
<th>Hormones</th>
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<tr>
<td>Melatonin</td>
<td>• Sleep deprivation decreases melatonin production, which decreases leptin and increases ghrelin production</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>• Estrogen suppresses appetite</td>
</tr>
<tr>
<td></td>
<td>• Imbalance estrogen/progesterone ratio can trigger intense food cravings</td>
</tr>
<tr>
<td>Cortisol</td>
<td>• Sustained high levels can lead to intense cravings and binge eating</td>
</tr>
</tbody>
</table>
Appetite Regulation

Stomach → ↑Ghrelin → POMC CART → Hypothalamus → Satiety

Fat → ↓Leptin → NPY AgRP → Hypothalamus → Hunger

Gut → ↑PYY →
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
Leptin Resistance

Leptin levels peak too early, causing intense food cravings.

Leptin Resistance: (the signal that enough food has been eaten is not received). Intense food cravings.

Minimal Amount of Fat Burning (40%)

Food is eaten after dinner.

Digestion of food and calorie storage.

No prime fat burning time, thus prone to weight gain.

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 tolylfluanid and other endocrine disruptors
- Bisphenol A (BPA)
Leptin Modulation

Increase:
- Insulin
- Cortisone
- Estrogens

Decrease:
- Adrenaline
- Male hormones
- Growth hormone
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 overdoses 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

http://www.drritamarie.com/go/ResistinFunctionalRoles
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
✓ 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 effects 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 levels.
- **Coffee** associated with high adiponectin and low leptin levels.
- 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

*Nutritional intervention to reduce the n-6/n-3 fatty acid ratio increases adiponectin concentration and fatty acid oxidation in healthy subjects. Eur J Clin Nutrition. 2007.*

✓ Adiponectin as a marker for metabolic syndrome

Resources and References

✓ http://www.drritamarie.com/go/AppetiteControl
✓ http://www.drritamarie.com/go/NeuropeptidesFoodIntake
✓ http://www.drritamarie.com/go/OrexinHypocretin
✓ http://www.drritamarie.com/go/AWeightyMatter
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✓ http://www.drritamarie.com/go/BPAasObesogen
Resources and References

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- http://www.drritamarie.com/go/EatingForPleasureOr Calories