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Gut Feelings: Decoding the Signals that Control Appetite

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The Innovators
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Obesity Trends* Among U.S. Adults

(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)
The Obvious Equation

\[ E_i = E_e \]

\[ E_i + (-E_e) = 0 \]
$E_i > E_e \rightarrow E_s$
“It is very injurious to health to take in more food than the constitution will bear, when, at the same time one uses no exercise to carry off this excess. . .
For as aliment fills, and exercise empties the body, the result of an exact equipoise between them must be to leave the body in the same state they found it, that is, in perfect health.”

Hippocrates
470 BC - 377 BC
Are there specific changes in food intake that correlate with the increase in overweight and obesity in human and non-human animals?

Many animals, including humans, eat much of their food as clearly defined meals. For people in the US, meal size has increased.
Increased rates of obesity are correlated with increased meal size

Data from Young and Nestle, 2002
But wait, there’s more!

20 Years Ago
- 333 calories
- 210 Calories
- 628 Calories

Today
- 590 calories
- 610 Calories
- 250 Calories
- 1450 Calories

Calorie Difference: 822 calories
Lifting weights a 130 lb person can burn about 822 calories in 4.8 hours.
Increased meal size, often imposed by restaurant portion size, appears to be a major determinant of excess energy intake and weight gain in people (See for example Orlet Fisher et al., 2003; Diliberti et al., 2004).

Increased meal size is associated with increased food intake and weight gain in most if not all rodent models of obesity (See for example Thomas and Mayer, 1978; Farley et al., 2004).
Elucidating the controls of meal size is important for understanding the control of food intake and its contribution to the pathogenesis of obesity.

Where do physiological signals that control meal size arise?
Ingested energy passes through distinct body compartments all of which provide signals that control food intake.
GI tract may detect the quantity and quality of ingested food directly.
Meal termination (satiation) is delayed when food does not accumulate in GI tract.
Intestinal nutrient infusion mimics natural satiation
Vagus nerve directly connects GI tract with brain

Vagus nerve directly carries sensory signals directly from internal organs to the brain.

About 16,000 sensory fibers in each vagus nerve.

Close to 70% of vagal sensory fibers innervate the gastrointestinal tract.

Vagal sensory neuron cell bodies located in nodose ganglia.
Vagal Afferent Fibers Carry Both Mechanical and Chemical Signals from the GI Tract to the Brain.
GI tract secretes peptide hormones that provide satiation signals to brain.

Submucosa:
Note nerve fiber
GI hormone secretion is triggered by nutrients in the intestine.
Some examples of GI peptides that contribute to control food intake:

- Cholecystokinin (CCK)
- Glucagon-related peptide -1 (GLP-1)
- Peptide YY
Injection of exogenous CCK reduces meal size and CCK-induced meal size reduction is mediated by the vagus nerve.
CCK is secreted into the blood in response to some intestinal nutrients.
Reduction of meal size by nutrients in the intestine is mediated by the vagus nerve.
Reduction of meal size by nutrients, such as long chain fatty acid, depends on CCK-1 receptors.
Summary

• CCK, a peptide hormone secreted by the intestine contributes to meal termination.

• Reduction of meal size by both CCK and nutrients that stimulate CCK secretion depends on vagal sensory neurons that connect the GI tract with the brain.

• CCK1 receptor activation is necessary for reduction of meal size by nutrients in the intestine

BUT,

Can changes in CCK signaling lead to obesity?

Learning from the CCK1 receptor deficient rat
CCK Does Not Reduce In Food Intake in CCK Receptor Mutant Rats

Covasa and Ritter 2001
Reduction of Meal Size by Intestinal Nutrients is Attenuated CCK1 Receptor Mutant Rats

Covasa and Ritter 2001
Increased Meal Size Leads to Obesity of CCK1 Receptor Mutant Rats
SUMMARY

CCK and nutrients in the small intestine reduce meal size by a process that depends on CCK1 receptors and vagal sensory innervation of the GI tract.

Rats that do not detect CCK eat larger meals and become obese.

Do other signals that control food intake interact with CCK?
All Body Energy Compartments Provide Signals That Control Food Intake
Leptin: Secreted by Fat Cells

Plasma leptin concentration proportional to adiposity

Leptin decreases meal size
Leptin Reduces Food Intake and Body Weight When Injected into the Brain and Might Interact With CCK Signals Centrally
Enhanced reduction of food intake and body weight by CCK acting peripherally and leptin acting in the brain

Matson and Ritter 1999, 2000
Leptin reduces food intake by reducing meal size.

Leptin reduces food intake by reducing meal size.
Does Leptin Reduce Meal Size by Interacting With CCK at Vagal Sensory Neurons?
Recording from nodose neurons that innervated specific target organs

Fluorescent latex beads
Most CCK Responsive Vagal Sensory Neurons Innervate Stomach or Intestine

Overall:
- No CCK Response: 35% CCK
- CCK Response: 65%

Stomach:
- No CCK Response: 74% CCK
- CCK Response: 26%

Duodenum:
- No CCK Response: 70% CCK
- CCK Response: 30%

Peters et al., 2006
Colocalization of Leptin and CCK Responsiveness in Vagal Sensory Neurons

Overall:
- Leptin Only: 11%
- Neither: 54%
- 21% CCK Only
- 14% CCK/Leptin

Stomach:
- 26%
- 32%
- 42%

Duodenum:
- 19%
- 12%
- 38%
- 31%

Peters et al., 2006
Celiac Arterial Infusion

- NTS
- Nodose Nanglia
- Stomach
- Duodenum
- Aorta
- Celiac Artery
Contrast radiograph of a celiac arterial infusion

- catheter
- fundic
- hepatic
- celiac a.
- L. gastric
- splenic

2 cm
Celiac arterial leptin infusion reduces meal size

% Reduction of Intake

Celiac Arterial

- 1 µg
- 3 µg
- 10 µg

Right Atrial

- 1 µg
- 3 µg
- 10 µg

* Significant difference
Celiac arterial leptin and CCK cooperate to reduce meal size.

Celiac Arterial

- Leptin 1 µg
- CCK 90ng
- Both

Right Atrial

- Leptin 1 µg
- CCK 90ng
- Both

% Reduction of Sucrose Intake
To Summarize

- Peptide hormones, like CCK, comprise satiation signals between GI tract and brain.
To Summarize

- Effects of other controllers of food intake, like the fat cell hormone, leptin, may exert some of their effects by enhancing signals from the GI tract to reduce meal size.
Mimicking or enhancing signals from GI hormones may provide a means to intervene to control food intake and weight gain.
Questions?
Coming Up

The Innovators lecture series
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