OBESITY CONUNDRUM 1:
Is There Evidence That a Food Solution Can Impact Overweight Through Biological Mechanisms: Appetite, Satiety and Energy Balance

Stephen C. Woods
University of Cincinnati

IFT Summit, New Orleans, 2004
The Dilemma

Kg

Decades
In the last three decades, American men increased their caloric intake by 7% and American women by 22%.
Energy Balance Equation

Intake
- Hunger
- Satiety
- Nutrient Absorption

Expenditure
- Metabolic Rate
- Thermogenesis
- Activity
Accuracy!

Energy Intake in a Year

955,570 calories

Gaining 1 pound (0.45 kg) in a year

~4000 calories

Error of 0.4%, or

11 calories/day
THE PUZZLE

If energy homeostasis is regulated so precisely,

• Does this imply the existence of a “set point?”

• Is the control system overwhelmed by environmental factors?
Evidence suggests that there is a body weight range rather than a body weight set point.

Upper and lower boundaries are genetically and ontogenetically determined.
The control system over energy homeostasis is complex, relying upon several types of signals.

MW Schwartz, SC Woods et al., *Nature*, 2000
MEALS

“Meals are the fundamental unit of food intake.”

GP Smith
MEALS

“Meals are the fundamental unit of food intake.”

GP Smith

• Factors that control when meals will occur are distinct from factors that control when meals will end;

• i.e., different signals control meal initiation and meal size.
CONTROL OF MEALS

• There is scant evidence that meal initiation is controlled by metabolic or hormonal signals.
CONTROL OF MEALS

• There is scant evidence that meal initiation is controlled by metabolic or hormonal signals.

The best evidence is that under normal circumstances, meal initiation is based upon learned associations, convenience or the social situation.
CONTROL OF MEALS

• There is scant evidence that meal initiation is controlled by metabolic or hormonal signals.

• There is compelling evidence that meal cessation (meal size) is controlled by preabsorptive signals from the gastrointestinal system.
CONTROL OF MEAL SIZE

FOOD INTAKE --> SENSOR

GUT

GASTROINTESTINAL PEPTIDES
“SATIETY FACTORS”

CHOLECYSTOKININ (CCK)
BOMBESIN FAMILY (GRP, NMB)
GLUCAGON

METABOLIC EFFECTS

(+)

(-)
Putative Satiety Factors:

- Cholecystokinin (CCK)
- Peptides in the bombesin family
  - Bombesin, GRP, Neuromedin B
- Apolipoprotein A-IV (apo A-IV)
- Peptide YY (PYY)
- GLP-1, enterostatin, amylin, glucagon, somatostatin

- Ghrelin
Reduction of Meal Size by CCK

From: J Gibbs & GP Smith, 1976

30-Min Food Intake

DOSE

From: J Gibbs & GP Smith, 1976
Satiety Signals:

• Secreted during meals, create a sensation of fullness or satiety

• Reduce meal size without causing malaise

• Interact with other controllers of meal size
Features of satiety signals:

• Most are made in both the GI tract and the brain.
Features of satiety signals:

• Most are made in both the GI tract and the brain.

This includes CCK, bombesin peptides, somatostatin, PYY, apo-A-IV and GLP-1, as well as ghrelin.
Features of satiety signals:

- Most are made in both the GI tract and the brain.
- They are efficacious in humans.
## Reducions of Meal Size in Humans Administered IV CCK

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Δ from Control</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>-3%</td>
<td>Kissileff, AJCN, 1981</td>
</tr>
<tr>
<td>Obese Men</td>
<td>-24%</td>
<td>Pi-Sunyer, PB, 1982</td>
</tr>
<tr>
<td>Men</td>
<td>-39%</td>
<td>Muurahainen, PB, 1988</td>
</tr>
<tr>
<td>Men, Women</td>
<td>-32%</td>
<td>Muurahainen, AJP, 1991</td>
</tr>
<tr>
<td>Men, Women</td>
<td>-8%</td>
<td>Geary, AJP, 1992</td>
</tr>
<tr>
<td></td>
<td>-6%</td>
<td>Geary, AJP, 1992</td>
</tr>
<tr>
<td></td>
<td>-32%</td>
<td>Geary, AJP, 1992</td>
</tr>
<tr>
<td>Obese Women</td>
<td>-31%</td>
<td>Geary, AJP, 1992</td>
</tr>
<tr>
<td>Men, Women</td>
<td>-20%</td>
<td>Lieverse, Gut, 1995</td>
</tr>
<tr>
<td>Men</td>
<td>-21%</td>
<td>Ballinger, Clin Sci, 1995</td>
</tr>
<tr>
<td>Men</td>
<td>-7%</td>
<td>Gutzwiller, AJP, 2000</td>
</tr>
</tbody>
</table>
IV CCK is More Effective at Reducing Meal Size in Men and Women After Eating a Standard Preload

Features of satiety signals:

• Most are made in both the GI tract and the brain.
• They are efficacious in humans.
• **Blocking their action leads to increased meal size.**
The CCK-A Receptor Antagonist, Loxiglumide (22 µMol/kg, iv), increases Caloric Intake in Men

Adapted from Beglinger C, Am J Physiol Regul Integr Comp Physiol 2001;280:R1149-54
Chemical and physical information is integrated in vagal sensory nerves as well as in the brain to control meal size.

Hormones, Nutrients

Vagus

Nodose Ganglion

Δ Food Intake

Forebrain

Hindbrain
CCK released from cells in the duodenum acts locally on CCK-A receptors on vagal afferent nerves that project to the hindbrain.
The effects of CCK and stomach stretch are integrated in vagal afferent fibers.
The effects of CCK and stomach stretch are integrated in vagal afferent fibers.
The effects of CCK and stomach stretch are integrated in vagal afferent fibers.
Knocking out CCK-A receptors, vagal transmission, or hindbrain relay nuclei attenuates CCK-induced satiety.
Gastric ghrelin increases food intake, and the effect is dependent upon an intact vagus nerve.
Adiposity Signals

Hindbrain

Forebrain

\( \Delta \) Food Intake

Vagus

Habits, Social Factors, Stress and Emotions, Learning, etc.

Satiety Signals
Can foods be used to increment endogenous CCK (or other satiety signals), leading to reduced meal size?
Can foods be used to increment endogenous CCK (or other satiety signals), leading to reduced meal size?

- Soybean trypsin inhibitor (SBTI) stimulates CCK and inhibits ghrelin secretion.
- Potato proteinase inhibitor (POT II) stimulates CCK secretion.
- Phenylalanine (stimulates CCK secretion).
- Other (green tea, calcium [milk], water, etc.)
Is mimicking or triggering CCK or other satiety signals a worthwhile strategy for the food industry?
CCK REDUCES THE SIZE OF EVERY MEAL

PERCENT OF CONTROL

West et al., AJP 246:R776 1984
CCK INCREASES THE
NUMBER OF MEALS

PERCENT OF CONTROL

West et al., AJP 246:R776 1984
CCK, GIVEN ALONE, HAS NO NET EFFECT ON FOOD INTAKE OR BODY WEIGHT IN FREELY FEEDING RATS

PERCENT OF CONTROL

MEAL SIZE

MEAL NUMBER

DAILY INTAKE

West et al., AJP 246:R776 1984
The control system over energy homeostasis is complex, relying upon several types of signals.
Humoral Regulation of Adiposity

CNS Regulatory Mechanisms

Food Intake, Energy Expenditure

“Adiposity Hormones”

Stored Calories
CONTROL OF BODY FAT

• Strong evidence that key signals reach the brain via the blood

• Adiposity Hormones
  * Insulin
Pancreatic insulin secretion is directly proportional to the size of the fat mass.
Obese Humans Secrete More Insulin in Proportion to Adiposity

CONTROL OF BODY FAT

• Strong evidence that key signals reach the brain via the blood

• Adiposity Hormones
  * Insulin
  * Leptin
Leptin secretion is directly proportional to the size of the fat mass.
Serum Leptin is Increased in Obesity

Increased Insulin or Leptin

Decreased Food Intake and Increased Energy Expenditure
Increased Insulin or Leptin

Increased Insulin or Leptin

 Decreased Food Intake and Increased Energy Expenditure

INSULIN


LEPTIN

Seeley, Horm Metab Res, 1995
Decreased Insulin or Leptin Action

Increased Food Intake and Decreased Energy Expenditure
Decreased Insulin or Leptin Action

Increased Food Intake and Decreased Energy Expenditure

McGowan, *Behav NSci*, 1985

Coleman, *Diabetologia*, 1972
Humoral Regulation of Adiposity

CNS Regulatory Mechanisms

Food Intake, Energy Expenditure

Insulin, Leptin

Stored Calories
The adiposity hormones, leptin and insulin, enter the hypothalamic arcuate nucleus and stimulate α-MSH/CART neurons while inhibiting NPY/AgRP neurons, thus activating catabolic pathways while inhibiting anabolic pathways.
The control system over energy homeostasis is complex, relying upon several types of signals.
Features of satiety signals:

• Most are made in both the GI tract and the brain.
• They are efficacious in humans.
• Blocking their action leads to increased meal size.
• Their efficacy is enhanced when adiposity signals are elevated.
IVT insulin dose-dependently reduces body weight over 6 days (g) in rats

Riedy et al., P&B, 58: 755,1995
Subthreshold insulin increases the satiating effect of IP CCK

% of Baseline Intake

- Con
- Ins
- CCK
- Ins + CCK

* Ins: 0.5 mU/day
  CCK: 4 μg/kg

Riedy et al., P&B, 58: 755,1995
Why are insulin and leptin called “adiposity signals,” and CCK and other GI peptides called “satiety signals?”
ADIPOSITY SIGNALS

M Chavez et al., Behav Neurosci, 1995
ADIPOSITY SIGNALS

BODY WEIGHT

TIME

CONTROL/SALINE i3vt

INSULIN i3vt

M Chavez et al., *Behav Neurosci*, 1995
M Chavez et al., *Behav Neurosci*, 1995
ADIPOSITY SIGNALS

BODY WEIGHT vs TIME

- CONTROL/SALINE i3vt
- INSULIN i3vt
- Food Restriction

M Chavez et al., *Behav Neurosci*, 1995
ADIPOSITY SIGNALS

BODY WEIGHT

TIME

CONTROL/SALINE i3vt

INSULIN i3vt

Return to ad lib food

M Chavez et al., *Behav Neurosci*, 1995
M Chavez et al., *Behav Neurosci*, 1995
ADIPOSITY SIGNALS

BODY WEIGHT

TIME

CONTROL/SALINE i3vt

INSULIN i3vt

M Chavez et al., Behav Neurosci, 1995
ADIPOSITY SIGNALS

M Chavez et al., *Behav Neurosci*, 1995
Effect of CCK

**Control/Saline i3vt**

**Insulin i3vt**

Food Intake

100%

* * * *

100%

*
Satiety signals:

Reduce meal size comparably
  • In lean animals
  • In genetically obese animals
  • In diet-induced obese animals

Have minimal effects on body weight
Adiposity signals:

Reduce body weight by enhancing the effect of satiety signals on each meal.

Have to be increased locally in the brain or else decreased systemically, and on a chronic basis, to be efficacious.

Leptin  (Prevention of weight regain)
Insulin  (Mimetics)
MW Schwartz, SC Woods et al., *Nature*, 2000
What are the best targets for intervention by the food industry?
Meal-Related Signals
Sight and Smell

Taste
Sight and Smell

Taste

Stomach Signals (Ghrelin, GRP, Stretch)
Sight and Smell

Taste

Stomach Signals (Ghrelin, GRP)

Duodenal Signals (CCK)
Sight and Smell

Taste

Stomach Signals (Ghrelin, GRP)

Duodenal Signals (CCK)

Lower Intestinal (PYY, Apo A-IV GLP-1)
Sight and Smell

Taste

Stomach Signals (Ghrelin, GRP)

Duodenal Signals (CCK)

Lower Intestinal (PYY, Apo A-IV GLP-1)

Pancreatic Signals (Amylin)
Sight, smell, palatability, mouth feel
Gastric and duodenal signals
Ileal signals
Ileal Transposition

GLP-1, PYY, Apo A-IV
Ileal Transposition

A short segment of ileum is transposed anteriorly such that chyme stimulates it earlier in the sequence of digestion.
Ileal Transposition (IT)

IT causes a small but reliable loss of weight.
Ileal Transposition

IT rats eat less food.
IT rats make and secrete more GLP-1.
Ileal Transposition

IT rats make and secrete more PYY.
What are the best targets for intervention by the food industry?

Perhaps foods or food additives could be developed that stimulate the ileum early during meals.
The control system over energy homeostasis is complex, relying upon several types of signals.

MW Schwartz, SC Woods et al., *Nature*, 2000
Possible Food Approaches

1. Foods/nutrients that uniquely influence satiety signals
   a. Soybean trypsin inhibitors
      West
      CCK-1 KO; half-lives
   b. Density a la Rolls

2. Foods/nutrients that uniquely influence adiposity signals
   a. GLP-1/Apo A-IV

3. Foods/nutrients that mimic the effects of bypass

4. Foods/nutrients that reduce cephalic responses
Why the mouth isn’t the place

DeCastro  People don’t eat food that they Perceive as unpalatable

Sham eating:  Internal signals must arise distal To the stomach