Integrative Regulation of Food Intake: The Role of Reward and Hedonic Aspects

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• I was previously employed by the University of Washington and Columbia University.
Each day, each of us must address several important questions regarding our food intake.

When to eat?
What to eat?
How much to eat?

While some of the answers are conscious decisions, many are not.
This presentation will deal with when we eat and how much we eat, with a focus upon the two major subdivisions of eating, homeostatic vs. non-homeostatic and how they interact in the brain.
Why do we eat?

• To provide necessary energy for the body

• Concept of homeostasis

• Is our food intake matched to our energy expenditure?
• Alternatively, do we eat for non-homeostatic reasons?

• How do homeostatic and non-homeostatic influences interact?
• Social reasons
• Stress
• Other
Homeostatic Controls

Insulin, Leptin, Glucose

Hypothalamus

Hindbrain

Behavior
Both food and drugs of abuse activate circuits in both types of controls. There is considerable overlap, and perhaps interference, between the two. or
Homeostatic Controls

Non-Homeostatic Controls

Hindbrain

Behavior

Drugs of Abuse

Palatable Food

Sex

Lateral Hypothalamus (LHA)

Reward

Orexin

Pay Attention

Dopamine

Reward

Drugs of Abuse

Palatable Food

Sex
The Dilemma

Decades

Kg
Key points about obesity

• It’s not a novel condition.

• Its incidence is increasing, and has been called an epidemic.
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• It is thought by many to reflect a failure of regulation.
Key points about obesity

• It’s not a novel condition.

• Its incidence is increasing, and has been called an epidemic.

• It is thought by many to reflect a failure of regulation.

• It is usually associated with increased food intake.
Energy balance equation

Intake
- Hunger
- Satiation
- Nutrient
- Absorption

Expenditure
- Metabolic rate
- Thermogenesis
- Activity
Ad-lib controls

Gavage overfed

Gavage normal-fed

Gavage underfed

Free-Feeding Resumed

Body weight (g)

Days

IL Bernstein, SC Woods, PSEBM, 1975
Accuracy!

Energy intake in 1 year
955,570 calories

Gaining 1 pound (0.45 kg) in 1 year
~4000 calories

Error of 0.4% or
11 calories/day*

*
Data such as these compellingly support the concept that food intake has a strong homeostatic influence that tends to maintain body weight (body fat) relatively constant over long intervals.
Thus, there are two apparently conflicting points of view. Experimental evidence in animals and humans suggests that body weight is tightly regulated; in contrast, population evidence says that average body weight is gradually increasing.

This reflects a fundamental tension between homeostatic and non-homeostatic controllers of food intake.
What determines **when** we eat, especially when food is always available?

- Habit
- Convenience
- Opportunity
- Social factors
What determines how much we eat during a meal?
Important Point about the Control of Meals

• Factors that control when meals will occur differ from factors that control when meals will end.

• Different signals control meal initiation and meal size.
• For most instances of food intake in humans and experimental animals, meal initiation is not controlled by metabolic or hormonal signals.

• Under normal circumstances, meal initiation is based upon learning, habits, convenience, or the social situation.

• There is compelling evidence that meal cessation (meal size) is controlled in part by signals from the gastrointestinal tract.
What is known of the factors that influence meal size?

In the 1970s, GI hormones, and especially peptide hormones, were thought to be likely mediators of food intake, and in 1973, it was reported that exogenous administration of the gut peptide, CCK (cholecystokinin), which is secreted during meals, reduces meal size.
This experiment was the first to implicate metabolic hormones in the control of food intake, and it ushered in the modern era of research on the energetics of eating.

J Gibbs et al., *JCPP*, 84:488, 1973
Control of meal size

FOOD INTAKE → (-) GUT → (+) GASTROINTESTINAL PEPTIDES “SATIATION SIGNALS” → (+) e.g., CHOLECYSTOKININ (CCK)

SENSOR → (+) METABOLIC EFFECTS → (+)
Reduction of meal size by CCK

30-Minute Food Intake

After J Gibbs & GP Smith, 1976
Putative satiation factors

- Cholecystokinin (CCK)*
- Bombesin family: bombesin, GRP, neuromedin B
- GLP-1*
- Glucagon, oxyntomodulin
- Peptide YY (PYY)*
- Amylin* (plus Leptin)*
- Apolipoprotein A-IV (apo A-IV)*, enterostatin, somatostatin
- Ghrelin*
Features of satiation signals

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

• Reduce meal size without causing malaise
Features of satiation signals

• They are efficacious in humans
### Reduction 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>
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<tr>
<td>Obese Men</td>
<td>-24%</td>
<td>Pi-Sunyer, PB, 1982</td>
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<tr>
<td>Men</td>
<td>-39%</td>
<td>Muurahainen, PB, 1988</td>
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<td>Men, Women</td>
<td>-32%</td>
<td>Muurahainen, AJP, 1991</td>
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<tr>
<td>Men, Women</td>
<td>-32%</td>
<td>Geary, AJP, 1992</td>
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<tr>
<td>Men</td>
<td>-8%</td>
<td>Geary, AJP, 1992</td>
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<tr>
<td>Men</td>
<td>-6%</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>
Features of satiation signals

• 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 2001;280:R1149-R1154.
Satiation signals

• Can they be used to treat obesity?
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

CONTROL   CCK

MEAL NUMBER

CONTROL   CCK

DAILY INTAKE

CONTROL   CCK

West et al., AJP 246:R776 1984
The Peptide-Signal Model of Food Intake

Satiation signals are relayed to the hindbrain mainly via the vagus nerves.
Adiposity signals circulate in the blood and enter the brain at the hypothalamus.
Humoral signal regulation of adiposity

CNS Regulatory Mechanisms

Food Intake, Energy Expenditure

Adiposity Hormones (Insulin & Leptin)

Stored Calories
Adiposity signals act by increasing the potency of satiation signals.

Control Food Intake

CCK

Homeostatic Controls

Adiposity Signals: Insulin, Leptin

Hypothalamus

Hindbrain

Behavior

Satiation Signals: CCK, etc.
This homeostatic model of food intake makes it seem overly deterministic.
Non-Homeostatic Influences on Food Intake

Social

Emotional

Hedonic/Reward

Cognitive/learned

Past experience

MW Schwartz, SC Woods et al., *Nature*, 2000
Non-homeostatic signals also act by increasing the potency of satiation signals.
And adiposity signals in turn alter the potency of non-homeostatic signals.
Sight and Smell

Meal-Related Signals

Stomach Signals (Ghrelin, GRP, Stretch)

Duodenal Signals (CCK)

Distal Intestinal Signals (PYY, Apo A-IV, GLP-1)

Pancreatic Signals (Amylin)

Adiposity-Related Signals (Leptin, Insulin, Adiponectin)

FAT
Ghrelin

- Increases before meals
- Via CNS, primes GI tract for meal
- Increases smell sensitivity
- Makes food taste better
- Enhances reward value of food
- Stimulates eating
Homeostatic Controls

Hypothalamus

Arcuate Nucleus

Orexin, Glutamate

Lateral Hypothalamus (LHA)

Brainstem

Behavior

Non-Homeostatic Controls

Amygdala, Accumbens, etc.

Dopamine

Highly Palatable Food
Taste

LHA

NPY

Food Intake

Orexin,
Glutamate

Dopamine/
Reward

Taste

ARC
Within 2 seconds of tasting a highly palatable food, the signal reaches the arcuate nucleus and stimulates increased eating via increased stimulation of NPY cells.
Take-away points:
The homeostatic controls over food intake are probabilistic, not fixed.

Non-homeostatic factors, and especially reward circuits, can overwhelm the otherwise rigorous controls over food intake and body weight.

Drugs of abuse can co-opt both homeostatic and non-homeostatic circuits.