Neural Systems Involved in Food Intake: An Integrated Overview

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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.
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?

• Hedonics
  • How do homeostatic and non-homeostatic influences interact?

• Other
Homeostatic Controls

Insulin, Leptin, Glucose

BRAIN

Hypothalamus

Brainstem

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

Anxiety, social situation, learning, hedonics, etc.
The Dilemma

Kg

Decades
Key points about obesity

- It’s not a novel condition.
- Its incidence is increasing, and has been called an epidemic.
Key points about obesity

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

*
Thus, there are two apparently conflicting points of view. Clinical and experimental evidence 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.
2. How do we eat?

- Meals
- What is the pattern of meals?
- Does the pattern matter?
- Nibblers vs. gorgers
What is known of the factors that influence food intake?

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.
What determines when we eat?

- Habit
- Convenience
- Opportunity (hedonics)
What determines how much we eat during a meal?

- Satiation
- Satiety
- Variety and palatability
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
Control of meals

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

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

- There is compelling evidence that meal cessation (meal size) is controlled in part by preabsorptive signals from the gastrointestinal system.
This experiment was the first to implicate metabolic hormones in the control of food intake, and it ushered in the age of peptides with regard to research on energy homeostasis.

J Gibbs et al., *JCPP*, 84:488,1973
Satiation signals are relayed to the hindbrain mainly via the vagus nerves.

MW Schwartz, SC Woods et al., *Nature*, 2000
Control of meal size

GASTROINTESTINAL PEPTIDES
“SATIATION SIGNALS”

e.g., CHOLECYSTOKININ (CCK)
Reduction of meal size by CCK

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

• Blocking their action leads to increased meal size
Features of satiation signals

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

• They are efficacious in humans
Satiation signals

• Can they be used to treat obesity?
CCK REDUCES THE SIZE OF EVERY MEAL

PERCENT OF CONTROL

MEAL SIZE

100

50

CONTROL   CCK

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

CONTROL     CCK     CONTROL     CCK     CONTROL     CCK

West et al., AJP 246:R776 1984
Adiposity signals circulate in the blood and enter the brain at the hypothalamus

MW Schwartz, SC Woods et al., *Nature*, 2000
This negative feedback model of body fat regulation is also consistent with a homeostatic interpretation.
The Homeostatic Model of Food Intake

Other Influences on Food Intake

Non-Homeostatic Influences over Food Intake

Social

Circadian

Past experience

Cognitive/learned

Non-Homeostatic Influences over Food Intake

Non-homeostatic feeding

- Non-homeostatic feeding occurs for reasons other than caloric balance.
- E.g. taste, texture, palatability, learned meal initiation, incentive and social context.

Cota et al, 2006
Caloric Status Regulates Reward

- Cocaine Self-Administration
- Relapse to Cocaine
- Cocaine Conditioned Place Preference
- Food Conditioned Place Preference

Metabolic Factors Regulate Reward

- Insulin
- Leptin
- Melanocortins
- Ghrelin
- Orexin
Non-Homeostatic Feeding

"Dessert Effect" then.

<table>
<thead>
<tr>
<th>Food Deprivation</th>
<th>Chow</th>
<th>Chow</th>
<th>2^{nd} hopper (test meal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hrs</td>
<td>1 hr</td>
<td>1 hr</td>
<td>1 hr</td>
</tr>
</tbody>
</table>

Systemic Injection
Non-Homeostatic Feeding

Choi et al., (2010) Neuroscience
Orexin, the PVT and Dopamine

- Orexin is required for drug-induced plasticity in VTA DA neurons (Borgland et al., 2006)

- Intra-VTA orexin increases NAcc DA (Narita et al., 2006)

- Nicotine activates PVT-projecting orexin neurons (Pasumarthi and Fadel, 2008)

- Orexin neurons are activated by cues associated with food (Harris et al., 2005; Choi et al., 2010)

- Orexin plays a role in promoting food reward-related behaviors (Choi et al., 2010)
Systemic administration of orexin receptor antagonist decreases high fat intake in sated rats

Choi et al., (2010) Neuroscience
PVT OX1R knockdown decreases high fat intake in sated rats

![Bar graph showing food intake in CHOW and HFD conditions with S.C. and OX1R KD groups]

- CHOW
  - 1st hr.
  - 2nd hr.
- HFD
  - S.C.
  - OX1R KD

Food Intake (kcal)
Orexin is sufficient and necessary for promoting PR responding for food rewards

Orexin-A

Vehicle

Choi et al., (2010) Neuroscience
Context-dependent expectation of chocolate activates the LH

Control Meal Fed Choc.-cond.

% of Control (c-Fos IR cells)

0 100 200 300

Control Meal Fed Choc.-cond.

Choi et al., (2010) Neuroscience
Intra-PVT administration of orexin-A increases dopamine levels in the NAcc
What about adiposity signals?
Effects of HF diet on DA turnover

**NAcc Dopamine Turnover**

- Chow
- HFD

**OFC Dopamine Turnover**

- Chow
- HFD

Davis et al., 2008
VTA leptin regulates DA activity and food intake

Hommel et al., 2006
Fulton et al., 2006

Hommel et al., 2006
Fulton et al., 2006
Homeostatic Controls

Brainstem

Hypothalamus

Behavior

Adiposity Signals: CCK, etc.

Non-Homeostatic Controls

Brainstem

Amygdala, Accumbens, etc.

Behavior

Anxiety, social situation, learning, hedonics, etc.

Satiation Signals: CCK, etc.
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.

• Likely involves increased intake of palatable foods.
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