Body weight, obesity, and the brain

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Janet Tung
Blaming the Brain for Obesity: Integration of Hedonic and Homeostatic Mechanisms

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The brain plays a key role in the controls of energy intake and expenditure, and many genes associated with obesity are expressed in the central nervous system. Technological and conceptual advances in both basic and clinical neurosciences have expanded the traditional view of homeostatic regulation of body weight by mainly the hypothalamus to include hedonic controls of appetite by enough to compete with other behaviors and had to be learned and passed to future generations.

Such a high-energy throughput also requires a large gastrointestinal (GI) tract capable of efficiently digesting and absorbing necessary nutrients. This is particularly true when high physical activity is combined with low dietary energy density and a massive brain, as in early hominids.
What is obesity and why should we care?

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<th>WEIGHT lbs</th>
<th>lbs</th>
<th>kgs</th>
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</table>
36% of Americans are obese

over 100 million people

health risks, costs
BEFORE

AFTER

AFTER AFTER
Is there a “set point” for body weight?

LATERAL HYPOTHALAMIC LESIONS AND BODY WEIGHT

FIG. 1. Body weights of control and LH-lesioned rats under restricted and ad lib feeding conditions.

Mitchel & Keesey, Phys. & Behav. 1977
regulatory defense of body weight
regulatory defense of body weight

**What tools does the body have?**

- Nutrient sensing system
- Nutrient monitoring system
- Energy storage and use
  - hormones, neurotransmitters
  - cell composition
  - resting metabolism
- Internal signal processing
- External signal processing
energy homeostasis: what kind of system?

linear dynamics

nonlinear (complex adaptive) system
complex adaptive systems

- non-linear dynamics
- system configuration
- open system: system and external environment
- attractor state
- response to perturbation
- bifurcation

Huh, Arch. Pharm. Res 2018
complex adaptive systems

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Boing, G., Systems 2016
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Lee et al, PLoS Biol. 2006
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Fig. 1a. Three-dimensional stability landscape with two basins of attraction showing, in one basin, the current position of the system and three aspects of resilience, L = latitude, R = resistance, Pr = precariousness.

Walker et al. 2004
complex adaptive systems

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Westley, et al. 2011
complex adaptive systems

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body weight regulation as complex system

Figure 1. The brain uses nutritional information from both outside and inside the body before, during, and after ingestive behavior. During the initiation phase, attention may be shifted to ingestive behavior because of hunger or an opportunity to consume a highly rewarding food item in the absence of metabolic hunger. During the procurement phase, unconditioned and conditioned stimuli from food and food cues interact through the external senses with the cognitive, emotional, and executive brain. During the consumatory phase, interoceptive signals from taste and the gastrointestinal tract reaching the “metabolic” brain guide the relatively stereotypical processes of digestion, transport, and absorption. Anticipatory reflexes shaped by prior experience thereby help, keeping regulated parameters within optimal limits. Finally, during the postigestive or metabolic phase, signals from the gut and organs that can store and/or metabolize energy, such as adipose tissue and liver, inform the brain about the metabolic consequences of the meal, providing reward from satisfaction and generating episodic memorial representations of the entire meal for future reference. By integrating external and internal information, the brain can regulate...
regulatory defense of body weight

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regulatory defense of body weight

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Possible parameters:
- nutrient responsiveness
e.g., sweet tooth

Degrees of freedom:
e.g., ratio of sweet to umami receptors

- Visual
- Olfactory
- Taste
regulatory defense of body weight

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  • Cellular: AMPK, mTOR
  • Gut taste receptors, et al.
  • endocrine hormones
  • Leptin and adipokinds
  • Myokines
  • FGF-21

Possible parameters:
e.g., hormone production rate;
myokine production rate

Degrees of freedom:
e.g., receptor and
hormone prevalence &
efficacy
regulatory defense of body weight

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- Internal signal processing
- External signal processing
Energy storage and use

Figure 2. Basomedial hypothalamic neurons as master integrators of internal and external nutritional information to achieve allostatics. AGRP/NPY hunger neurons translate hunger signals from both the internal milieu and hedonic feedback into sustained and complete appetitive and consumatory ingestive behavior by programming a downstream neural network that increases the incentive or reward value of particular foods. While AGRP/NPY neurons could be thought of as the gas pedal, POMC/CART neurons represent the brake pedal, acting through parallel downstream pathways.
Energy expenditure

thermogenesis!
perturbation resistant system parameters and configuration

• System elements under genetic and epigenetic control
• E.g., receptor density and ratio
• Many parameters such as basal metabolic rate
• hormonal production
• cellular signaling
external influences

- Food availability; energy-dense foods
- Hedonic environment (food cues, food porn)
- Stress-induced overeating
- Mindless and habit-eating
A systems-oriented, multilevel model applied to the study of obesity. The contingent effects of risk regulators (i.e., embodiment, opportunity, and constraint) are shown with dotted arrows. "Causal" effects of biological and behavioral variables are shown with solid arrows. Feedback loops existing within grouped variables are not shown. Specific effects and multiple, time-ordered feedback loops between variables are not shown in order to reduce diagram complexity. Reprinted with permission from Elsevier (8).