Published in final edited form as:

Biol Psychiatry. 2017 May 01; 81(9): e73–e75. doi:10.1016/j.biopsych.2017.02.1177.

Eat to Live or Live to Eat? The Neurobiology of Appetite Regulation

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For the sin/ Of gluttony, damned vice, beneath this rain, / E'en as thou seest, I with
fatigue am worn

Dante, *Inferno*

Augustus Gloop! Augustus Gloop! The great big greedy nincompoop! How long
could we allow this beast/ To gorge and guzzle, feed and feast/ On everything he
wanted to

Roald Dahl, *Charlie and the Chocolate Factory*

From Dante's *Inferno* (1), composed in the 14th century, to Roald Dahl's *Charlie and the Chocolate Factory* (2), centuries of literature consistently portray obese characters as vile and unrestrained. Even today, the continued stigma associated with obesity may contribute to many biopsychosocial problems, including mental health disorders, substance use, and stress (3). As worldwide obesity rates rise (4) we are only now coming to appreciate the neurobiological underpinnings of what has often been construed as willful self-indulgence.

The regulation of eating is a complex neurophysiological process influenced by environmental, genetic, and hormonal factors. Appetite and feeding are controlled by two interacting systems: a homeostatic system, which ensures that a person gets enough calories to survive, and a hedonic system, which regulates the pleasure and reward aspects of eating. Key aspects of these systems are illustrated in Figure 1.

Homeostatic System

Imagine Tom Hanks' character from *Cast Away* (2000), stranded and starving on a desert island: how does his body—or any person's body for that matter—signal the homeostatic need for food and calories? The pathway begins in the arcuate nucleus of the hypothalamus. Two types of neurons, named after orexis (from Latin orexis [appetite] and Greek *órexís* [desire]), are housed here: orexigenic and anorexigenic neurons stimulate and suppress food-seeking behaviors, respectively. Arcuate nucleus neurons project to three other regions of the

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Disclosures: DAR is co-chair of the National Neuroscience Curriculum Initiative and reports no other financial interests or potential conflicts of interest. KRK and JJC report no biomedical financial interests or potential conflicts of interest.

hypothalamus: the paraventricular nucleus, which influences several regions that promote catabolism (including the thyroid system, cortisol system, and oxytocin); the ventromedial hypothalamus, which suppresses feeding behavior through the release of brain-derived neurotrophic factor; and the lateral hypothalamus, which stimulates our search for calorically dense food and promotes locomotor activity through melanin-concentrating hormone and orexin (5,6). These three nuclei of the hypothalamus work together to ensure that we eat (or do not eat) based on the signals received about the body's current needs.

Peripherally, three hormones contribute to the central regulation. Leptin is produced in adipose tissue and acts on receptors in the arcuate nucleus to promote satiety and heat production (5). Ghrelin is produced in the gastrointestinal track, increases hunger, decreases energy expenditure, and stimulates cortisol release (5). Cortisol mobilizes glucose to ensure that the body has sufficient energy to respond to an acute stressor. However, chronically elevated cortisol leads to a blunted leptin (satiety) response, increased desire for foods dense with sugar and fat (think comfort food), and the accumulation of abdominal fat (5,7).

Hedonic System

Though food consumption serves a homeostatic function, eating can also be an extraordinarily pleasurable experience (hence the neologism *foodgasm*). Our pleasurable response to food largely overlaps with the brain's core reward circuits (e.g., as involved in drugs and sex). These include the amygdala, an area associated with emotional learning; the ventral tegmental area, which contains dopaminergic neurons and signals motivation and reward seeking; the nucleus accumbens, centrally involved in reward learning; and the lateral hypothalamus, which coordinates these motivation signals and links the homeostatic system with the hedonic system (5).

Feeding behavior can be altered due to pathological functioning of either the homeostatic system or the hedonic system. Examples of appetite dysregulation across these different systems can be found in obesity, depression, anorexia nervosa, bulimia nervosa, and binge eating disorder.

Obesity

One manifestation of appetite malfunction is obesity. A striking example of our society's obsession with weight—and the extremes to which people will go to cure their obesity—is the reality TV show *The Biggest Loser*. Yet despite the contestants' intense investment in the process (and the additional support they received), a recent study found that after 6 years, many of these individuals regained much of the weight they had lost. Longitudinally, the participants demonstrated a slowing of their metabolic rates: an adaptation in which their bodies decrease energy expenditure to counter their weight loss (8). Frustratingly, these data suggest that obesity is more than a simple choice: motivation to lose weight is necessary but often not sufficient. One reason may be that many people with obesity exhibit leptin resistance, a concept similar to insulin resistance in diabetics (6). Leptin resistance occurs with chronically high circulating leptin levels due to excess adipose tissue. The response from the brain becomes blunted and leptin no longer produces the same degree of satiety

after a meal. The dopamine surge from food is also diminished, decreasing the sense of reward with eating (6). Thus, the cycle of obesity becomes difficult to pause or reverse, as the body does not respond to hunger and satiety signals properly.

Atypical Depression

In this issue of *Biological Psychiatry*, Milaneschi *et al.* (9) demonstrate a link between leptin resistance and atypical depression. Fascinating recent research has described the potential antidepressant properties of leptin. Moreover, this action may be dampened in a state of leptin resistance. Three theories have been proposed to explain the new findings: obesity-related leptin resistance may determine a vulnerability for depression; leptin dysregulation may be a consequence of weight increase due to the depression; or atypical depression and obesity-related leptin resistance may share the same genetic risk factors (9).

Anorexia Nervosa

On the opposite end of the spectrum, anorexia nervosa is an illness in which a person is somehow impervious to the drive to eat. Similar to obesity, multiple systems are at play, but a breakdown in cortisol feedback is particularly relevant. Cortisol levels are elevated in anorexia nervosa due to the stress of starvation. Under ordinary circumstances, this might lead to increased food consumption. But these patients develop both an aberrant reward system and a so-called fear of food that causes them to overcome this drive to eat (5,10). As cortisol increases locomotor activity patients become hyperactive, which further burns calories. The body then views this physical activity as a biological stressor and releases more cortisol in a vicious cycle. The malfunctioning reward pathway makes food an aversive stimulus while food restriction and physical activity become rewarding and even addicting (5).

Bulimia and Binge Eating Disorder

Two other eating disorders (EDs) also involve aberrant reward signaling in relation to food. Both disorders involve increased impulsivity—heightened reward sensitivity and impaired inhibitory control—which is maintained in the lateral prefrontal cortex (10). Bulimia nervosa patients have decreased inhibitory control in the lateral prefrontal cortex and possibly decreased reward responses to food leading to a compensatory binge. Binge eating disorder patients, on the contrary, show increased reward responsivity to food cues with an increased dopamine release in the dorsal striatum (10). Hyperresponsiveness to food rewards and cues likely leads to cravings that override the homeostatic feeding mechanisms. Low inhibitory control may increase sensitivity to the rewarding aspects of food, making it difficult to overcome the temptation to eat (4).

Hope for the Future

ED and obesity treatment has classically involved nutritional intervention, cognitive or behavioral therapies, and sometimes pharmacotherapy. Bariatric surgery for morbid obesity and hospitalization for severe EDs represent extreme interventions (4). As many people fail

to obtain a healthy weight despite these treatments, neurobiologically informed interventions could be invaluable.

The least invasive of these strategies is neurofeedback. This technology uses brain imaging, such as real-time functional magnetic resonance imaging, to provide patients moment-to-moment information about their brain activity to learn self-regulation techniques (4). Neurofeedback has shown some efficacy in targeting the reward and inhibitory systems and helping individuals to overcome environmental triggers and compensatory behaviors associated with overeating or EDs (4).

Transcranial magnetic stimulation and transcranial direct current stimulation have focused on the dorsolateral prefrontal cortex to enhance cognitive control of reward circuitry (as the hypothalamic circuitry described above is inaccessible with these technologies) (4). Vagus nerve signaling is reduced in obesity and vagus nerve stimulators may offer some benefit (4). Finally, deep brain stimulation, the most invasive form of neuromodulation, has been used to intervene specifically within the hypothalamus. In animal studies, lateral hypothalamic stimulation typically leads to appetite stimulation and weight gain, while ventromedial hypothalamic stimulation typically leads to appetite restriction and weight loss, consistent with the model described above (4). Safety and efficacy have not yet been demonstrated in human trials.

Neuromodulation is not yet a mainstream treatment for EDs and requires further research into technique, targets, and safety. However, an understanding of the relevant neurobiology will be essential to future treatments for these disorders.

In summary, both the homeostatic and hedonic systems play a role in feeding. Their interaction, along with other complexities not explored in this commentary, underscores appetite regulation in states of health and illness. Understanding the neurobiology of over- and undereating can reduce the stigma of these conditions, which have historically been seen as sins of volition.

Acknowledgments

This work was supported by the National Institutes of Health Grant Nos. R25 MH10107602S1 and R25 MH086466 07S1 (to DAR).

This commentary was produced in collaboration with the National Neuroscience Curriculum Initiative. We thank Dr. Melissa Arbuckle for her contribution as National Neuroscience Curriculum Initiative editor and Amanda Wang for her role in developing the figure.

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Figure 1.

The left side shows homeostatic regulation, depicting how peripheral signals are received by and processed in the hypothalamus. Purple arrows represent orexigenic and anorexigenic projections from the arcuate nucleus. The right side shows the major reward pathway structures that interact with this homeostatic regulation of appetite through the lateral hypothalamus. GI, gastrointestinal.