REVIEW ARTICLE

NUTRITION IN MEDICINE
Julie R. Ingelfinger, M.D., and Clement D. Lee, M.D., *Editors*

The Physiology of Hunger

Alessio Fasano, M.D.

From the Division of Pediatric Gastroenterology and Nutrition, Mass General for Children and Harvard Medical School, Boston (A.F.); the Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston (A.F.); and the European Biomedical Research Institute of Salerno, Salerno, Italy (A.F.). Dr. Fasano can be contacted at afasano@mgh.harvard.edu.

N Engl J Med 2025;392:372-81.
DOI: 10.1056/NEJMra2402679

Hunger is an ancestral and evolutionary survival instinct; its importance is evident in the complex and redundant pathways involving all five senses that regulate it.[1,2] Historically, when humans were hunter-gatherers with an unpredictable food supply, the regulation of hunger primarily involved maintaining a metabolic equilibrium between caloric intake and expenditure. The advent of agriculture 12,000 years ago increased the availability of affordable, energy-dense, palatable food, resulting in a substantial effect on the evolutionary physiology of hunger that had been shaped by the preceding 2 million years.[3,4] A wealth of basic and translational research on the pathophysiology of hunger has revealed the complexity of the processes that regulate eating habits and are influenced by socioeconomic, cultural, psychological, and behavioral factors.

The relative stability of body weight over time in any given person suggests a highly sophisticated metabolic machinery that is capable of regulating a multitude of variables, both predictable (e.g., basal metabolic rate) and unpredictable (e.g., quality and quantity of food ingested, thermic effect of food, macronutrient composition, and level of physical activity). However, this precise regulatory process, which was evolutionarily primed to favor the overconsumption of calories (and permissive of a positive caloric balance to allow fat accumulation as an energy reservoir in hunter-gatherers)[5] is now having negative medical consequences.

Mechanisms Controlling Hunger

To appreciate the intricate mechanisms at play in the regulation of hunger, it is necessary to distinguish between hunger — the physiological impulse to eat that is triggered by starvation (acute energy deprivation) in order to maintain energy balance — and appetite, or hedonic hunger, with food intake driven by pleasure rather than by metabolic necessity. In either situation, eating requires exquisite coordination between the brain and the gut, one of the most sophisticated examples of the gut–brain axis cross-talk. Functionally and evolutionarily, hunger can be characterized through three distinct but highly interconnected mechanisms: homeostatic, hedonic, and microbiota-driven (Fig. 1).

Homeostatic Hunger

Homeostatic hunger, which is the most ancestral mechanism controlling hunger, involves the brain–gut axis — specifically, the hypothalamus–gut axis. This model, first described by Walter Cannon in 1929, characterized hunger as a passive process triggered by nutrient depletion and alleviated by nutrient absorption.[5] There is now solid evidence, in both animal models and humans, that the hypothalamic circuitries controlling hunger are regulated by sensory signals stemming mostly from the gastrointestinal tract. An empty stomach stimulates both the

KEY POINTS

THE PHYSIOLOGY OF HUNGER

- Hunger is controlled by redundant neuroendocrine circuitries that maintain metabolic balance.
- Homeostatic hunger is triggered by food deprivation and involves neuroendocrine, endocrine, and metabolic signals that convey the need to eat.
- Conversely, hedonic hunger occurs in the absence of acute caloric need. By increasing the availability of food, agriculture has favored hedonic hunger over homeostatic hunger.
- The composition and function of gut microbiota may influence hunger circuitries; however, their exact role in controlling food intake remains to be established.
- New knowledge of the physiology of hunger offers new possible therapeutic targets to modulate food intake in pathologic conditions, including obesity and anorexia nervosa.

vagus nerve and secretion of ghrelin, considered the "appetite hormone." These afferent neurologic and endocrine signals are relayed to the hypothalamus, conveying the need to eat. Afferent vagal fibers stimulate the release of dopamine, which reinforces the hunger signal, and ghrelin increases appetite through the activation of its receptor, GHSR1a, in the hunger-sensing, γ-aminobutyric acid (GABA)–producing neurons of the hypothalamus, which in turn produce agouti-related peptide (AgRP).[6,7] AgRP neurons are rapidly inhibited by the sensing of food through vision, smell, or taste.[8]

In addition to ghrelin, hypoglycemia appears to trigger hunger by regulating the activity of specific hypothalamic neurons that respond to serum glucose levels. Aside from neuroendocrine signals, motilin-induced interprandial phase III gastrointestinal contractions seem to control hunger and regulation of food intake in humans, in both healthy and disease states, through a cholinergic pathway.[9,10] Luminal stimuli, such as bitter tastants, have been identified as modulators of motilin release, affecting hunger and food intake.[9]

With food intake, an equally intricate pathway repressing hunger is initiated by gastric distention, as detected by specific mechanoreceptors of tension, stretch, and volume that then relay signals to the hindbrain through vagal and spinal nerves.[11] This initial satiety signal is subsequently reinforced by the presence of specific amino acids and fatty acids in the gastrointestinal tract, leading to hunger suppression (Fig. 1A). Gastric emptying, as well as the osmotic load within the gastrointestinal tract, provides further information related to meal quality and quantity and contributes to early satiety. A variety of gastrointestinal hormones, such as glucagon-like peptide 1 (GLP-1), cholecystokinin, and peptide YY (PYY), are secreted in the presence of digested food within the proximal small intestine and lead to medium-term satiety through the generation of inhibitory signals in the brain.[12] Late satiety is ultimately reached when, at the completion of digestive processes, plasma levels of amino acids, glucose, and insulin increase. Such metabolic satiety, along with sensory signals and the integration of all these processes in the central nervous system (CNS), completes the cycle of homeostatic hunger control (Fig. 1A).

HEDONIC HUNGER

Whereas homeostatic hunger is typical of people who experience food deprivation, hedonic (pleasure-driven) hunger is characterized by a desire to eat in the absence of acute caloric need (Fig. 1B). In homeostatic hunger, the tightly regulated hunger–satiety balance is adjusted to maintain metabolic homeostasis, preventing excessive calorie intake. In the presence of substantial food availability, however, hedonic or reward cortical circuitries can supersede hypothalamic control of energy balance, leading to ingestion of energy-dense, high-fat, and high-sugar food not out of necessity but for pleasure.[13] Hedonic hunger is also influenced by both negative and, more frequently, positive emotions, resulting in individual differences in eating behavior.[14] For example, anger, fear, sadness, and depression are often associated with excessive consumption of sweet food.[15]

It is well established that babies are prone to favor sweet and salty tastes as compared with bitter and sour tastes,[16] most likely as part of an adaptive mechanism to consume safe food such

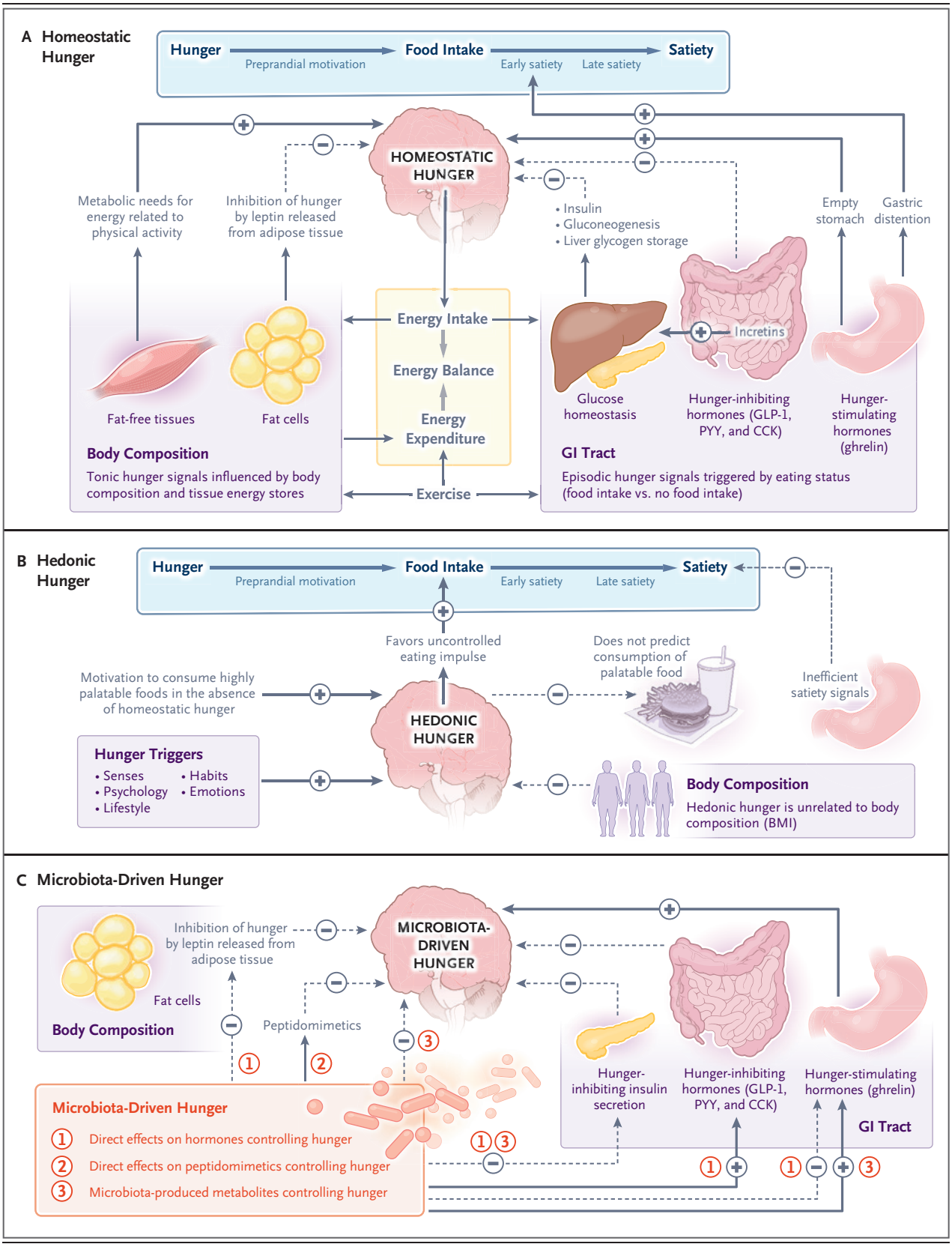

Figure 1 (facing page). Mechanisms Controlling Hunger and Satiety.

Homeostatic, hedonic, and microbiota-dependent hunger circuitries control the initiation of food intake through direct interaction with specific areas of the brain, stimulation of hormone-controlling hunger, and microbiota-generated substances that affect the host hunger pathways (Panels A, B, and C, respectively). With food intake, counterbalanced mechanisms controlling early, medium, and late satiety are activated to reach a metabolic balance between caloric intake and expenditure. An imbalance of this hunger–satiety equilibrium may lead to eating disorders and their metabolic complications. CCK denotes cholecystokinin, GI gastrointestinal, GLP-1 glucagon-like peptide 1, and PYY peptide YY.

Table 1. Proposed Pathways for Microbiota-Driven Hunger.*

Pathway	Species	Reference
Signaling		
Leptin	Human	Le Chatelier et al.,[31] Massier et al.[32]
GLP-1	Human	Parnell and Reimer[33]
PYY	Human	Cani et al.[34]
Ghrelin	Human	Hume et al.[35]
Insulin	Human, mouse	Le Chatelier et al.,[31] Li et al.[36]
NPY	Mouse	Li et al.[36]
Microbiota-derived metabolite		
Butyrate	Mouse	Liu et al.,[37] Li et al.[38]
Acetate	Mouse	Perry et al.[39]
Propionate	Human	Chambers et al.,[40] Li et al.[38]
Succinate	Human	Serena et al.[41]
Indole	Mouse	Chimerel et al.[42]
Microbial-produced GABA	Human, mouse	Liu et al.,[43] Kootte et al.[44]
Microbiota-derived peptidomimetic		
Leptin-like	Human	Fettisov et al.[45]
Ghrelin-like	Human	Fettisov et al.[45]
PYY-like	Human	Fettisov et al.[45]
ClpB (α-MSH-like)	Human, mouse	Arnoriaga-Rodríguez et al.,[46] Breton et al.[47]

* ClpB denotes caseinolytic peptidase B, GABA γ-aminobutyric acid, GLP-1 glucagon-like peptide 1, MSH melanocyte-stimulating hormone, NPY neuropeptide Y, and PYY peptide YY.

as human milk, which is sweet and favors better satiety control than baby formulas.[17] This bias toward fatty, sweet, and salty food in the context of a Western lifestyle in which food availability is not a limiting factor may, in part, be responsible for obesogenic trends, particularly among children. Indeed, Western parents are more prone to let children eat palatable, energy-dense food ("permissive eating"), despite their detrimental effect on health, out of concern that more nutritionally healthful choices such as vegetables, fruits, or fiber-rich food may be rejected, resulting in undernutrition.[18]

Eating patterns are also influenced by taste preferences, as well as pleasurable sensations in the brain reward system that are triggered by the anticipation of consuming palatable foods.[1,19,20] In addition, socioeconomic factors (the generally lower cost of unhealthful food as compared with healthful food), cultural beliefs (obesity as a sign of health and wealth in many societies), and religious practices (food restrictions in certain religions) can modify hedonic hunger. Furthermore, food advertisements may initiate dopamine release from the reward-related brain areas and incite eating-related thoughts and desires. In addition, endogenous cannabinoids, endogenous opioid pathways,[21] and orexin signaling[22] are involved in the hedonic reward of food intake. The clinical outcome of the consumption of highly rewarding, calorie-dense food is excessive weight gain (resulting in overweight or obesity), which is associated with major disorders, including cardiovascular diseases, hypertension, and type 2 diabetes mellitus.[23,24]

The Power of Food Scale (PFS), developed in 2009 to quantify hedonic hunger, assesses the psychological effects of living in food-abundant environments and has yielded insights into four related domains.[25] First, the scale accurately measures the motivation to consume palatable foods; both men and women with high PFS scores direct their visual attention toward palatable food. Functional neuroimaging in such persons has shown activation of processing areas in the visual cortex when they are exposed to images or descriptions of palatable food. In contrast, those with low PFS scores do not have the same activation of neuronal circuitries connecting regions associated with hunger, craving, and food-seeking behavior.

Second, persons with high PFS scores do not necessarily consume more palatable food, despite the motivation to do so. Evidence suggests

that hedonic hunger alone is insufficient to predict food intake but might favor overconsumption if coexistent with other individual characteristics, such as poor impulse control. Thus, hedonic hunger is probably only weakly or inconsistently associated with food intake. Accordingly, the third domain, body-mass index (BMI) is also not substantially related to hedonic hunger. One explanation is that in a society of abundance and constant exposure to palatable food, people think about and crave delicious food, irrespective of their BMI. However, a 2021 weight loss study suggests that at least in a subgroup of persons, a reduction in hedonic hunger is associated with a lower BMI at 12 months.[26] Finally, hedonic hunger as measured by the PFS score appears to be related to disordered eating. Limited studies suggest that there is a link between hedonic hunger and an uncontrolled eating impulse and that the degree of hedonic hunger is associated with the magnitude of the eating impulse.

Whereas homeostatic hunger is a straightforward survival instinct triggered by a single stimulus (acute calorie deprivation), hedonic hunger is multifactorial and extremely complex, involving learning, cognition, and memory. Thus, hedonic hunger is very difficult to tackle on a population basis but should be approached with the use of individualized strategies based on the factor (or factors) at play in any given person.

MICROBIOTA-DRIVEN HUNGER

Gut microbiota are symbiotes that provide the host with protection from pathogens and contribute to immune system programming and control of key metabolic functions, including energy metabolism. In addition, microbiota provide the host with energy through the release of enzymes and trophic metabolites (e.g., short-chain fatty acids).[27] Since hunger is highly dependent on bidirectional gut–brain communication, gut microbiota also influence host hunger circuitries.[28] Several mechanisms that involve both systemic and nervous pathways, either by indirectly affecting hunger through hormones or by producing metabolites that directly affect hunger, have been elucidated. Most research in this area is descriptive, involving animal models, or based on cross-sectional clinical studies with small sample sizes. Clinical trials aimed at modulating gut microbiota to reduce hunger as a means of weight management have generated conflicting data.[29,30] Therefore, the exact role of microbiota in affecting human host hunger requires further clarification. Some examples of the mechanisms involved in microbiota-driven hunger are reviewed below, and proposed species-specific mechanisms are listed in Table 1.

MICROBIOTIC EFFECTS ON HUMAN HORMONES CONTROLLING HUNGER

Microorganisms are capable of influencing the release of hunger-controlling hormones (e.g., ghrelin, leptin, and insulin) produced by the gut, adipose tissue, and pancreas (Fig. 1C). Decreased microbiota diversity (a sign of dysbiosis) has been associated with higher serum leptin concentrations in both lean and obese persons.[31] In obese persons, increased gut permeability can facilitate the passage of microbiota components from the gut lumen into host adipose tissue, altering energy metabolism through inhibition of leptin signaling and resulting in dysglycemia and, in some cases, type 2 diabetes mellitus.[32] Prebiotics from gut microbiota, including inulin and oligofructose, appear to inhibit hunger by increasing the synthesis of GLP-1 and PYY while concomitantly inhibiting ghrelin production in both lean and obese adults.[33,34] In studies involving children with obesity, however, supplementation of oligofructose-enriched inulin led to decreased food intake, which was associated with subsequent increased ghrelin concentrations but did not affect GLP-1, PYY, or insulin pathways.[35] Like leptin and ghrelin, insulin can modify hunger by affecting AgRP neurons[48] and can be influenced by gut microbiota. Indeed, reduced gut bacteria diversity has been associated with increased insulin resistance.[31] In addition, in a study involving obese mice, probiotics altered gut microbial composition and inhibited hunger by decreasing insulin resistance and inhibiting neuropeptide Y expression.[36] Inconsistent results between studies involving adults and those involving children may be due to age-related differences but are most likely due to differences in study design and interpretation.

MICROBIOTA-DERIVED METABOLITES CONTROLLING HUNGER

Microbiota-derived metabolites (postbiotics) are key signaling mediators of the microbiota–gut–

brain axis and contribute to hunger. Short-chain fatty acids, including butyrate, propionate, and acetate, are the biologic products of bacterial fermentation of poorly digestible polysaccharides (e.g., fibers). After binding to free fatty acid receptor 3 and G protein–coupled receptor 41 in pancreatic islets, short-chain fatty acids are capable of stimulating homeostatic hunger by favoring ghrelin-related signaling and inhibiting insulin secretion.[37,39] However, there is also evidence that short-chain fatty acids can suppress hunger by binding free fatty acid receptor 2 and G protein–coupled receptor 43, which can lead to the release of GLP-1, PYY, insulin, and leptin.[38,40,49,50] Besides stimulating homeostatic hunger, short-chain fatty acids — and specifically, colonic propionate — may reduce hedonic hunger through inhibition of CNS reward circuits.[51] Finally, acetate produced by colonic bacteria may cross the blood–brain barrier and directly inhibit AgRP neurons in the hypothalamus.[52]

Succinate is another biologic product of colonic bacteria that can affect host energy homeostasis through hunger control. A study showed that persons with obesity have increased levels of circulating succinate, and dietary interventions for weight loss in such persons are associated with changes in microbiota composition and reduced circulating succinate concentrations.[41] However, experiments in animal models have yielded inconsistent results.[53,54]

Indole, another microbiota-derived metabolite, can suppress hunger by stimulating the release of GLP-1.[42] In addition, a study showed that indole stimulates tryptophan production, which in turn causes release of 5-hydroxytryptamine from enteroendocrine cells.[55] Multiple studies have shown that 5-hydroxytryptamine plays a pivotal role in suppressing hunger by improving insulin sensitivity and affecting AgRP neurons.[56-58]

Gut microbiota also produce GABA from dietary glutamate. GABA is one of the key molecules mediating gut–brain communication, including hunger control through activation of AgRP neurons.[59-61] Persons with obesity have a decreased abundance of glutamate-fermenting gut microorganisms, with a corresponding increase in circulating glutamate levels,[43] findings that corroborate the role of glutamate in energy balance that has been shown in animal models.[44]

MICROBIOTA-DERIVED HUNGER CONTROL PEPTIDOMIMETICS

Several studies have shown that the gut microbiota can produce proteins (classified as peptidomimetics) that mimic the structure and function of hunger-controlling proteins such as PYY, ghrelin, and leptin.[45] One of the best examples of a bacterial peptidomimetic is caseinolytic peptidase B (ClpB), produced by *Escherichia coli*, which has an effect similar to that of the human host–produced hunger suppressor α-melanocyte–stimulating hormone (α-MSH).[46] Specifically, in vivo animal models have shown that like α-MSH, ClpB increases serum levels of GLP-1 and PYY and activates hypothalamic neurons that suppress hunger.[47] These data suggest that the gut microbiota can also suppress hunger through specific peptidomimetics.

GENETIC CONTROL OF HUNGER

Although the effect of socioeconomic, psychological, and cultural factors on eating behavior is clear, the role of genetics in influencing food preference, taste, and the quality and quantity of food intake appears to be less straightforward. Nonetheless, there are several examples of rare monogenic disorders that cause hyperphagia and obesity.[62] The Prader–Willi syndrome, a genetic condition associated with deletion of the 11-13q region of chromosome 15, is the prototypical example of a genetic disorder that can cause insatiable hunger and the development of severe obesity during childhood.[63] Children with the Prader–Willi syndrome have complications of severe obesity, including type 2 diabetes mellitus and cardiac failure, and they rarely survive beyond 25 to 30 years of age. Loss-of-function genetic variants of the leptin gene (*LEP*) on chromosome 7q31.3 or its receptor (*LEPR*) also lead to abnormal eating behavior, resulting in early-onset, severe obesity.[64,65] These rare forms of genetic obesity confirm the crucial role of specific pathways in hunger control and homeostasis. However, monogenic forms of obesity account for less than 7% of the cases of childhood obesity.[66]

CONSEQUENCES OF DYSREGULATED HUNGER CIRCUITRIES

A corollary of the complex and redundant network that controls hunger and satiety is that

dysregulation of the circuitries may lead to eating disorders, ranging from undereating (anorexia) to overeating (hyperphagia, obesity, and related metabolic disorders such as type 2 diabetes mellitus).[67,68] The increasing interest in the neurobiology of these disorders is fueled by their growing effect on public health.

Inappropriate and severe restriction of food intake, leading to dangerous weight loss and metabolic reprogramming, are the landmark features of anorexia nervosa, a condition affecting a large number of patients, particularly girls and young women, in industrialized countries. The behaviors seen in patients with anorexia nervosa can be conceptualized as an extreme form of the metabolic adaptation to starvation. Indeed, to preserve biologic functions that are paramount for survival (e.g., brain oxygenation and blood supply to the heart), there is both central and peripheral reprogramming of endocrine and neurologic signaling that controls energy balance, physical exercise, reproductive biology, bone metabolism, and feeding behavior. Paradoxically, ghrelin levels are increased in patients with anorexia nervosa, which suggests that chronic food restriction leads to compensatory attempts to stimulate hunger. Why this appropriate compensatory adaptation does not translate into increased hunger is unknown, but transient insensitivity to ghrelin and metabolic reprogramming have been proposed.[69,70] This paradox has engendered great interest and might ultimately lead to targets for therapeutic strategies.[69]

In addition to putatively aberrant peripheral signaling, patients with anorexia nervosa have altered brain function, characterized by deficits in dopamine and serotonin secretion, which control eating behavior or rewards and impulse control or neuroticism, respectively. Furthermore, patients with anorexia nervosa have inappropriate activation of the corticolimbic system, which controls appetite and fear, and decreased activity of the frontostriatal circuits, which regulate habitual behaviors.[70] Analysis of stool microbiome and metabolic profiles in patients with anorexia nervosa has revealed differences in composition and diversity of gut microbiota, as compared with healthy controls.[71] In addition, both animal models and clinical studies have suggested that gut dysbiosis, by increasing intestinal permeability, may influence the development of eating disorders[72,73] related to excessive trafficking of ClpB and lipopolysaccharide from the gut lumen into the systemic circulation.[74,75]

Excessive food intake, as discussed above, is becoming a major public health issue. According to the World Health Organization, one of eight persons worldwide had obesity in 2022, and during the past 30 years, the prevalence of obesity has doubled among adults and quadrupled among adolescents.[76] Data from the pediatric population are particularly alarming; worldwide, 37 million children under 5 years of age and more than 390 million children and adolescents 5 to 19 years of age are overweight or obese.[76] Persons with obesity, irrespective of age, are at increased risk for many serious diseases and health conditions, including high blood pressure, type 2 diabetes mellitus, osteoarthritis, psychological problems (e.g., anxiety, depression, and the effects of bullying and stigma), and low self-esteem, as compared with persons with healthy weight. In addition, obesity and its associated health problems have a substantial economic effect worldwide, with obesity-related medical care costing an estimated $173 billion annually in the United States.

Many health care, nutrition, physical, social, economic, and educational programs have so far failed to affect the increasing rates of obesity worldwide. New discoveries in the neurobiology of hunger, however, have led to the development of potential pharmacologic remedies for the problem. The most prominent example is the use of GLP-1 receptor agonists in the past two decades, starting with their initial approval by the Food and Drug Administration in 2005. GLP-1 receptor agonists have been shown to improve blood glucose control, reduce the risk of heart disease in patients with obesity, and help patients with overweight or obesity lose weight by suppressing hunger.[77]

However, the cosmetic use of these agents by celebrities, athletes, and, most concerning, adolescents without a medical indication could lead to unintended long-term adverse effects. Specifically for the pediatric population, GLP-1 receptor agonists have been shown to negatively affect growth and development, since they can cause a long-term imbalance between energy intake and expenditure, suppress appetite, have antihedonic effects, and cause fatigue.[78] These changes may translate into an improper balance between energy intake and energy expenditure

during a critical period of development in which calories are necessary not only for daily activities but also for growth. Furthermore, there are some reports on the misuse of GLP-1 receptor agonists among children with eating disorders and among adolescents involved in competitive sports with body-weight–based competitive groupings.[78]

IMPLICATIONS

In the past few years, we have gained substantial knowledge about the physiology of hunger, which opens the possibility of personalized treatments, population-based health strategies, and preventive interventions. In the United States, annual expenditures include $800 billion on food (30% of which is wasted), $14 billion in food advertising, and $456 million on health and fitness, totaling $814.5 billion in food and food-related costs. In addition, the cost of new drugs for weight control, such as the GLP-1 receptor agonists, will almost certainly further increase diet-related expenditures. According to the International Food Policy Research Institute, $100 billion annually is required to end world hunger, an eighth of what is spent on food-related costs in the United States. Policy changes toward addressing hunger may solve many nutrition-related health problems and make food production more sustainable and equitably distributed to benefit both industrialized and developing countries.

SUMMARY AND CONCLUSIONS

The mechanisms governing the physiology of hunger are multidimensional, complex, and still not completely defined. The progress made in this field in the past few years has allowed us to appreciate some of the mechanisms at play and the effect of evolutionary changes, particularly related to food procurement, on the pathophysiology of food intake. We should now capitalize on this knowledge to develop personalized interventions and preventive measures that promote metabolic balance and, ultimately, good health.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

1. Kringelbach ML, Stein A, van Hartevelt TJ. The functional human neuroanatomy of food pleasure cycles. Physiol Behav 2012;106:307-16.
2. Stevenson RJ, Boutelle K. Hunger, satiety, and their vulnerabilities. Nutrients 2024;16:3013.
3. Wells JCK, Stock JT. Life history transitions at the origins of agriculture: a model for understanding how niche construction impacts human growth, demography and health. Front Endocrinol (Lausanne) 2020;11:325.
4. Carey J. Unearthing the origins of agriculture. Proc Natl Acad Sci U S A 2023;120(15):e2304407120.
5. Cannon WB. Organization for physiological homeostasis. Physiol Rev 1929;9:399-431.
6. Cowley MA, Smith RG, Diano S, et al. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron 2003;37:649-61.
7. Andermann ML, Lowell BB. Toward a wiring diagram understanding of appetite control. Neuron 2017;95:757-78.
8. Betley JN, Xu S, Cao ZFH, et al. Neurons for hunger and thirst transmit a negative-valence teaching signal. Nature 2015;521:180-5.
9. Deloose E, Verbeure W, Depoortere I, Tack J. Motilin: from gastric motility stimulation to hunger signalling. Nat Rev Endocrinol 2019;15:238-50.
10. Deloose E, Vos R, Janssen P, et al. The motilin receptor agonist erythromycin stimulates hunger and food intake through a cholinergic pathway. Am J Clin Nutr 2016;103:730-7.
11. Cummings DE, Overduin J. Gastrointestinal regulation of food intake. J Clin Invest 2007;117:13-23.
12. Van Kleef E, Van Trijp JCM, Van Den Borne JJGC, Zondervan C. Successful development of satiety enhancing food products: towards a multidisciplinary agenda of research challenges. Crit Rev Food Sci Nutr 2012;52:611-28.
13. Hussain SS, Bloom SR. The regulation of food intake by the gut-brain axis: implications for obesity. Int J Obes (Lond) 2013;37:625-33.
14. Meule A, Vögele C. The psychology of eating. Front Psychol 2013;4:215.
15. Salerno A, Laran J, Janiszewski C. Hedonic eating goals and emotion: when sadness decreases the desire to indulge. J Consum Res 2014;41:135-51.
16. Birch LL, Fisher JO. Development of eating behaviors among children and adolescents. Pediatrics 1998;101:539-49.
17. Brown A, Lee M. Breastfeeding during the first year promotes satiety responsiveness in children aged 18-24 months. Pediatr Obes 2012;7:382-90.
18. Hennessy E, Hughes SO, Goldberg JP, Hyatt RR, Economos CD. Permissive parental feeding behavior is associated with an increase in intake of low-nutrient-dense foods among American children living in rural communities. J Acad Nutr Diet 2012;112:142-8.
19. Alonso-Alonso M, Woods SC, Pelchat M, et al. Food reward system: current perspectives and future research needs. Nutr Rev 2015;73:296-307.
20. Gutjar S, Dalenberg JR, de Graaf C, et al. What reported food-evoked emotions may add: a model to predict consumer food choice. Food Qual Prefer 2015;45:140-8.
21. Gosnell BA, Levine AS. Reward systems and food intake: role of opioids. Int J Obes (Lond) 2009;33:Suppl 2:S54-S58.
22. Katzman MA, Katzman MP. Neurobiology of the orexin system and its potential role in the regulation of hedonic tone. Brain Sci 2022;12:150.
23. Pereira MA, Kartashov AI, Ebbeling CB, et al. Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. Lancet 2005;365:36-42.
24. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr 2000;71:1455-61.

25. Espel-Huynh HM, Muratore AF, Lowe MR. A narrative review of the construct of hedonic hunger and its measurement by the Power of Food Scale. Obes Sci Pract 2018;4:238-49.

26. Mead BR, Boyland EJ, Christiansen P, Halford JCG, Jebb SA, Ahern AL. Associations between hedonic hunger and BMI during a two-year behavioural weight loss trial. PLoS One 2021;16(6):e0252110.

27. Fetissov SO. Role of the gut microbiota in host appetite control: bacterial growth to animal feeding behaviour. Nat Rev Endocrinol 2017;13:11-25.

28. van de Wouw M, Schellekens H, Dinan TG, Cryan JF. Microbiota-gut-brain axis: modulator of host metabolism and appetite. J Nutr 2017;147:727-45.

29. Álvarez-Arraño V, Martín-Peláez S. Effects of probiotics and synbiotics on weight loss in subjects with overweight or obesity: a systematic review. Nutrients 2021;13:3627.

30. Leong KSW, Jayasinghe TN, Wilson BC, et al. Effects of fecal microbiome transfer in adolescents with obesity: the gut bugs randomized controlled trial. JAMA Netw Open 2020;3(12):e2030415.

31. Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. Nature 2013;500:541-6.

32. Massier L, Chakaroun R, Tabei S, et al. Adipose tissue derived bacteria are associated with inflammation in obesity and type 2 diabetes. Gut 2020;69:1796-806.

33. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. Am J Clin Nutr 2009;89:1751-9.

34. Cani PD, Lecourt E, Dewulf EM, et al. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. Am J Clin Nutr 2009;90:1236-43.

35. Hume MP, Nicolucci AC, Reimer RA. Prebiotic supplementation improves appetite control in children with overweight and obesity: a randomized controlled trial. Am J Clin Nutr 2017;105:790-9.

36. Li X, Wang E, Yin B, et al. Effects of Lactobacillus casei CCFM419 on insulin resistance and gut microbiota in type 2 diabetic mice. Benef Microbes 2017;8:421-32.

37. Liu J-L, Segovia I, Yuan X-L, Gao Z-H. Controversial roles of gut microbiota-derived short-chain fatty acids (SCFAs) on pancreatic β-cell growth and insulin secretion. Int J Mol Sci 2020;21:910.

38. Li Z, Yi C-X, Katiraei S, et al. Butyrate reduces appetite and activates brown adipose tissue via the gut-brain neural circuit. Gut 2018;67:1269-79.

39. Perry RJ, Peng L, Barry NA, et al. Acetate mediates a microbiome-brain-β-cell axis to promote metabolic syndrome. Nature 2016;534:213-7.

40. Chambers ES, Viardot A, Psichas A, et al. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. Gut 2015;64:1744-54.

41. Serena C, Ceperuelo-Mallafré V, Keiran N, et al. Elevated circulating levels of succinate in human obesity are linked to specific gut microbiota. ISME J 2018;12:1642-57.

42. Chimerel C, Emery E, Summers DK, Keyser U, Gribble FM, Reimann F. Bacterial metabolite indole modulates incretin secretion from intestinal enteroendocrine L cells. Cell Rep 2014;9:1202-8.

43. Liu R, Hong J, Xu X, et al. Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention. Nat Med 2017;23:859-68.

44. Kootte RS, Levin E, Salojärvi J, et al. Improvement of insulin sensitivity after lean donor feces in metabolic syndrome is driven by baseline intestinal microbiota composition. Cell Metab 2017;26(4):611-619.e6.

45. Fetissov SO, Hamze Sinno M, Coëffier M, et al. Autoantibodies against appetite-regulating peptide hormones and neuropeptides: putative modulation by gut microflora. Nutrition 2008;24:348-59.

46. Arnoriaga-Rodríguez M, Mayneris-Perxachs J, Burokas A, et al. Gut bacterial ClpB-like gene function is associated with decreased body weight and a characteristic microbiota profile. Microbiome 2020;8:59.

47. Breton J, Tennoune N, Lucas N, et al. Gut commensal E. coli proteins activate host satiety pathways following nutrient-induced bacterial growth. Cell Metab 2016;23:324-34.

48. Loh K, Zhang L, Brandon A, et al. Insulin controls food intake and energy balance via NPY neurons. Mol Metab 2017;6:574-84.

49. Bolognini D, Barki N, Butcher AJ, et al. Chemogenetics defines receptor-mediated functions of short chain free fatty acids. Nat Chem Biol 2019;15:489-98.

50. Kimura I, Ozawa K, Inoue D, et al. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43. Nat Commun 2013;4:1829.

51. Byrne CS, Chambers ES, Alhabeeb H, et al. Increased colonic propionate reduces anticipatory reward responses in the human striatum to high-energy foods. Am J Clin Nutr 2016;104:5-14.

52. Frost G, Sleeth ML, Sahuri-Arisoylu M, et al. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. Nat Commun 2014;5:3611.

53. De Vadder F, Kovatcheva-Datchary P, Zitoun C, Duchampt A, Bäckhed F, Mithieux G. Microbiota-produced succinate improves glucose homeostasis via intestinal gluconeogenesis. Cell Metab 2016;24:151-7.

54. Mills EL, Pierce KA, Jedrychowski MP, et al. Accumulation of succinate controls activation of adipose tissue thermogenesis. Nature 2018;560:102-6.

55. Ye L, Bae M, Cassilly CD, et al. Enteroendocrine cells sense bacterial tryptophan catabolites to activate enteric and vagal neuronal pathways. Cell Host Microbe 2021;29:179-196.e9.

56. Nectow AR, Schneeberger M, Zhang H, et al. Identification of a brainstem circuit controlling feeding. Cell 2017;170(3):429-442.e11.

57. van Lingen M, Sidorova M, Alenina N, Klempin F. Lack of brain serotonin affects feeding and differentiation of newborn cells in the adult hypothalamus. Front Cell Dev Biol 2019;7:65.

58. D'Agostino G, Lyons D, Cristiano C, et al. Nucleus of the solitary tract serotonin 5-HT_{2C} receptors modulate food intake. Cell Metab 2018;28(4):619-630.e5.

59. Kim ER, Wu Z, Sun H, et al. Hypothalamic non-AgRP, non-POMC GABAergic neurons are required for postweaning feeding and NPY hyperphagia. J Neurosci 2015;35:10440-50.

60. Auteri M, Zizzo MG, Serio R. GABA and GABA receptors in the gastrointestinal tract: from motility to inflammation. Pharmacol Res 2015;93:11-21.

61. Krashes MJ, Shah BP, Koda S, Lowell BB. Rapid versus delayed stimulation of feeding by the endogenously released AgRP neuron mediators GABA, NPY, and AgRP. Cell Metab 2013;18:588-95.

62. Holsen LM, Zarcone JR, Brooks WM, et al. Neural mechanisms underlying hyperphagia in Prader-Willi syndrome. Obesity (Silver Spring) 2006;14:1028-37.

63. Greenswag LR. Adults with Prader-Willi syndrome: a survey of 232 cases. Dev Med Child Neurol 1987;29:145-52.

64. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997;387:903-8.

65. Clément K, Vaisse C, Lahlou N, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998;392:398-401.

66. Farooqi S, O'Rahilly S. Genetics of obesity in humans. Endocr Rev 2006;27:710-8.

67. Kaye WH, Wierenga CE, Bischoff-Grethe A, et al. Neural insensitivity to the effects of hunger in women remitted from anorexia nervosa. Am J Psychiatry 2020;177:601-10.

68. Watson HJ, Yilmaz Z, Thornton LM, et al. Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nat Genet 2019;51:1207-14.

69. Méquinion M, Langlet F, Zgheib S, et

al. Ghrelin: central and peripheral implications in anorexia nervosa. Front Endocrinol (Lausanne) 2013;4:15.
70. Wierenga CE, Bischoff-Grethe A, Melrose AJ, et al. Hunger does not motivate reward in women remitted from anorexia nervosa. Biol Psychiatry 2015;77:642-52.
71. Monteleone AM, Troisi J, Serena G, et al. The gut microbiome and metabolomics profiles of restricting and binge-purging type anorexia nervosa. Nutrients 2021;13:507.
72. Jésus P, Ouelaa W, François M, et al. Alteration of intestinal barrier function during activity-based anorexia in mice. Clin Nutr 2014;33:1046-53.
73. Mörkl S, Lackner S, Meinitzer A, et al. Gut microbiota, dietary intakes and intestinal permeability reflected by serum zonulin in women. Eur J Nutr 2018;57:2985-97.
74. Dominique M, Legrand R, Galmiche M, et al. Changes in microbiota and bacterial protein caseinolytic peptidase B during food restriction in mice: relevance for the onset and perpetuation of anorexia nervosa. Nutrients 2019;11:2514.
75. Cryan JF, O'Riordan KJ, Cowan CSM, et al. The microbiota-gut-brain axis. Physiol Rev 2019;99:1877-2013.
76. World Health Organization. Obesity and overweight. March 1, 2024 (https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight).
77. Ansari HUH, Qazi SU, Sajid F, et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists on body weight and cardiometabolic parameters in individuals with obesity and without diabetes: a systematic review and meta-analysis. Endocr Pract 2024;30:160-71.
78. Cooper DM, Rothstein MA, Amin A, Hirsch JD, Cooper E. Unintended consequences of glucagon-like peptide-1 receptor agonists medications in children and adolescents: a call to action. J Clin Transl Sci 2023;7(1):e184.