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Lateral Hypothalamic Control of Energy Balance

Gizem Kurt
Hillary L. Woodworth
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Lateral Hypothalamic Control of Energy Balance
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www.morganclaypool.com

ISBN: 9781615047659 paperback

ISBN: 9781615047666 ebook

ISBN: 9781615047673 hardcover

DOI: 10.4199/C00159ED1V01Y201711ISP079

A Publication in the

COLLOQUIUM SERIES ON INTEGRATED SYSTEMS PHYSIOLOGY: FROM MOLECULE TO FUNCTION TO DISEASE

Lecture #79

Series Editors: D. Neil Granger, LSU Health Sciences Center, and Joey P. Granger, University of Mississippi Medical Center

Series ISSN

ISSN 2154-560X print

ISSN 2154-5626 electronic

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ABSTRACT

Food and water are necessary for survival, but can only be obtained via ingestive behaviors (feeding, drinking, and moving). Survival thus depends on the ability of the brain to coordinate the need for water and energy with appropriate behaviors to modify their intake as necessary for homeostasis. However, the balance of these behaviors also inherently determines body weight, and imbalances contribute to the development of weight disorders, such as obesity and anorexia nervosa. The lateral hypothalamic area (LHA) of the brain is anatomically positioned to coordinate the sensation of osmotic and energy status with goal-directed ingestive behaviors necessary to maintain homeostasis and body weight, and, hence, may hold insight into the potential treatment for energy balance disorders. This volume reviews the essential role of the LHA for the control of body weight, from its historical description as a "feeding center" to the current view of this LHA as a cellularly heterogeneous hub that regulates multiple aspects of physiology to influence body weight. Furthermore, we evaluate how specific LHA populations coordinate certain metabolic cues and behaviors, which may guide the development of pathway-specific interventions to improve the treatment of energy balance disorders.

KEYWORDS:

lateral hypothalamic area, energy balance, body weight regulation, orexin, hypocretin, melanin concentrating hormone, neurotensin, ingestive behavior

Contents

CHAPTER 1

The Weighty Implications of the Lateral Hypothalamic Area in Energy Balance

1.1 HOMEOSTASIS AND BODY WEIGHT

Perhaps, the most fundamental theme of physiology is homeostasis: the maintenance of a relatively stable internal environment necessary to support life. Two essential components for homeostasis are adequate stores of energy (derived from caloric intake) and fluid (water), both of which are essential for cell, system, and bodily health. However, the very physiologic processes used to sustain life (e.g., respiration, thermogenesis, movement, digestion) constantly tap bodily reserves of energy and water so that they must be continually replenished. Because food and water cannot be synthesized within the body, they must be replaced via ingestion. Preservation of energy and fluid homeostasis, thus, requires that animals constantly assess their internal environment, detect need for energy and/or water, and then execute the appropriate feeding and/or drinking behaviors to obtain these resources from the environment. The feelings of hunger and thirst serve to communicate the body's need for food and water to the brain so that it can coordinate the appropriate ingestive behavior (feeding or drinking) to restore homeostasis. An important byproduct of this process is the regulation of body weight, which is a visible proxy for homeostasis and whether adequate resources are available to support bodily health. For example, fasting-induced hunger or dehydration-induced thirst increase the motivation to find and ingest food and water, respectively [1, 2]. Failure to obtain these resources results in acute weight loss that initially strengthens the drives to obtain them, and to avoid prolonged depletion of energy and fluid reserves that would compromise survival. Resource excess is coordinated with behavioral responses to limit intake: stomach fullness or increased body fat cue the cessation of feeding [3, 4], whereas plasma hypotonicity biases for salt versus water intake to restore fluid homeostasis [5]. Thus, individuals vigilantly monitor fluid and energy status and coordinate appropriate ingestive behaviors that impact body weight and survival. Although work over the

past decades indicates that the brain is crucial for orchestrating drive states, behavior, and body weight, the precise neural circuits underlying these processes remain incompletely understood. Herein, we will address the role of a particular part of the brain, the lateral hypothalamic area (LHA), in coordinating energy balance, homeostasis and, hence, in the physiology underlying health and survival.

1.2 WHAT IS ENERGY BALANCE AND HOW DOES IT RELATE TO HEALTH?

Energy homeostasis is often referred to and illustrated as "energy balance," to convey the interdependent relationship between energy intake and expenditure that determines body weight and health (Figure 1A). Energy intake consists of calories consumed through food and caloric-liquids, such as milk, juices, or sugar-laden sports drinks and soda. Energy expenditure refers to the calories that are consumed by the body to support basal metabolism and behavior, in the form of voluntary physical activity. For most individuals, energy expenditure is the sum of their resting metabolic rate (RMR), the thermic effect of feeding (TEF), and the thermic effect of activity (TEA) [6]. RMR comprises 60% to 75% of total energy expenditure and is the energy required by the body to perform basic physiologic functions, or more simply the "number of calories an individual would use if he/she stayed in bed all day." The TEF accounts for 10% of energy expenditure and is the energy required for digesting food. The TEA can account for 15% to 30% of an individual's energy expenditure and refers to the additional calories burned through volitional activity and exercise [6]. When energy intake exceeds expenditure, it creates a caloric surfeit, or "positive energy balance," which can be stored in the body as fat and lead to weight gain (Figure 1B). Conversely, when energy expenditure exceeds caloric intake, the body experiences a caloric deficit or "negative energy balance"; as a result, calories required to support survival are obtained from adipose reserves, leading to weight loss (Figure 1C).

At face value, energy balance appears to be a simple math equation, but its coordination is complex, requiring continuous communication between the periphery (to sense energy status) and the brain (to modulate energy intake and expenditure, as necessary). Energy balance is intimately tied to the idea of a body weight "set-point" wherein genetic and environmental factors determine an individual's body weight, which is defended through homeostatic mechanisms that compensate for positive or negative energy balance [7]. For example, in controlled over-feeding studies, total energy expenditure increases and appetite decreases as the body attempts to deplete the caloric surplus [8, 9]. Similarly, weight loss leads to increased

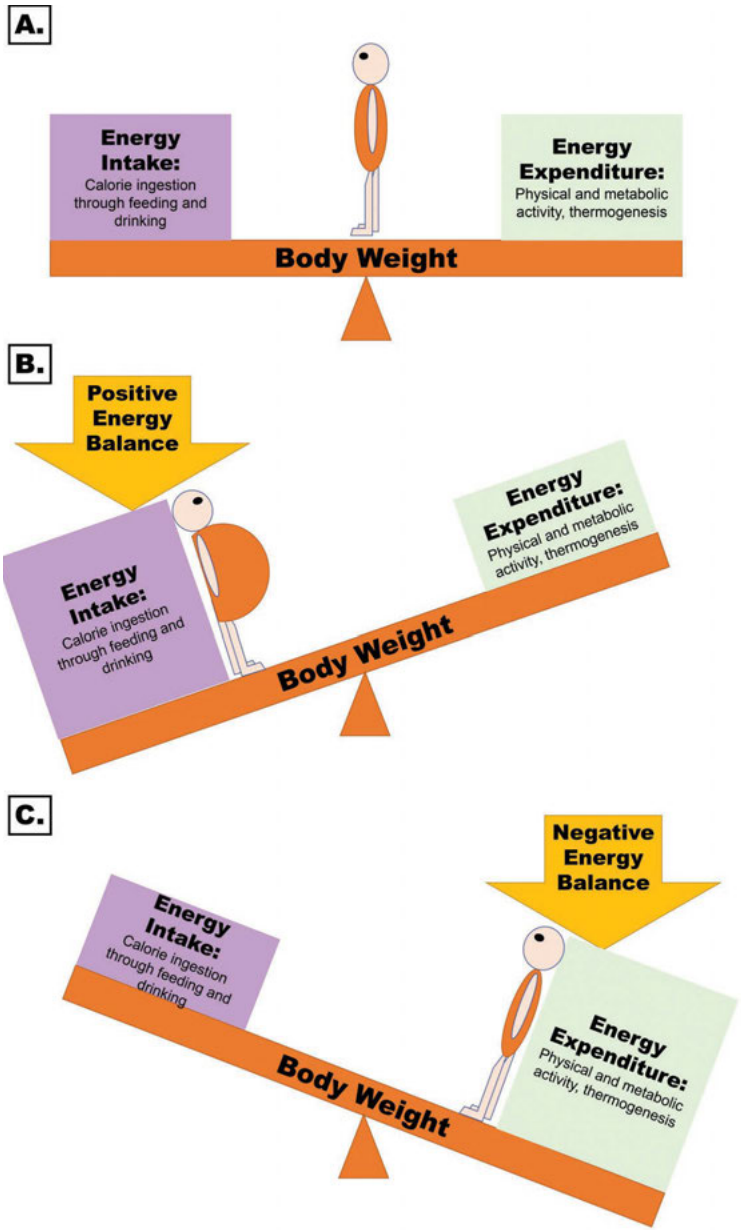

FIGURE 1: Energy Balance. (A) The interdependent relationship between energy intake and expenditure that determines body weight. (B) Positive energy balance with increased energy intake and decreased energy expenditure leading to weight gain. (C) Negative energy balance with decreased energy intake and increased energy expenditure leading to weight loss.

appetite and reduced energy expenditure that drives recovery of lost body weight and indeed, most people who lose weight gain it back [10–14]. Cota et al. provide a salient example of just how tightly the body coordinates energy balance: the average adult male uses around 900,000 calories per year and only gains (on average) one pound or 3600 extra calories during that time, which amazingly amounts to >99% accuracy in matching food intake with energy expenditure [15].

1.3 OBESITY IS A DISEASE OF DISRUPTED ENERGY BALANCE

Although energy balance is exquisitely fine-tuned in the short-term, small, incremental weight gain over years is thought to contribute to obesity. As such, the body weight set-point slowly drifts upward with time [7], and losing weight after being overweight or obese for several years is extremely challenging because the body strives to defend a heavier set-point [12, 13]. A prime example of this physiology comes from study of obese participants on the TV show "The Biggest Loser": contestants lost >120 pounds on average during the show, but 6 years later, individuals had regained approximately two thirds of the weight and their energy-expenditure was significantly decreased compared with what would be expected for their body weight [16]. Thus, overweight individuals who have lost weight are constantly battling increased hunger and reduced energy expenditure as their bodies defend their heavier weight set-point. This specific disruption of energy balance is a major health concern, as the worldwide prevalence of obesity and overweight has increased dramatically over the past decades [17, 18]. The United States of America (U.S.) is also experiencing an obesity epidemic [18, 19], with self-reported adult obesity rates exceeding 35% of the population in many states (Figure 2). Although geographic and socioeconomic factors may also play roles in the development of overweight and obesity [20], the incidence rates are high across demographics and regions of the U.S. Additionally, the growing occurrence of U.S. childhood and adolescent obesity (Figure 3) puts these individuals at risk for early development of chronic obesity-linked conditions (Figure 4), such as type-2 diabetes, cardiovascular disease, stroke, and cancer that require lifelong management and which can reduce lifespan [21, 22].

Despite the rising incidence of obesity and its negative impact on quality of life, there remain few medical strategies that have proven effective in maintaining long-term weight loss. The first-line prescription for weight reduction is diet and exercise, which has been capitalized by the U.S. weight loss industry, a market worth $60 billion in 2015 [23]. Although dieting individuals initially lose weight, most do not maintain the weight loss long-term [24]. A regimen

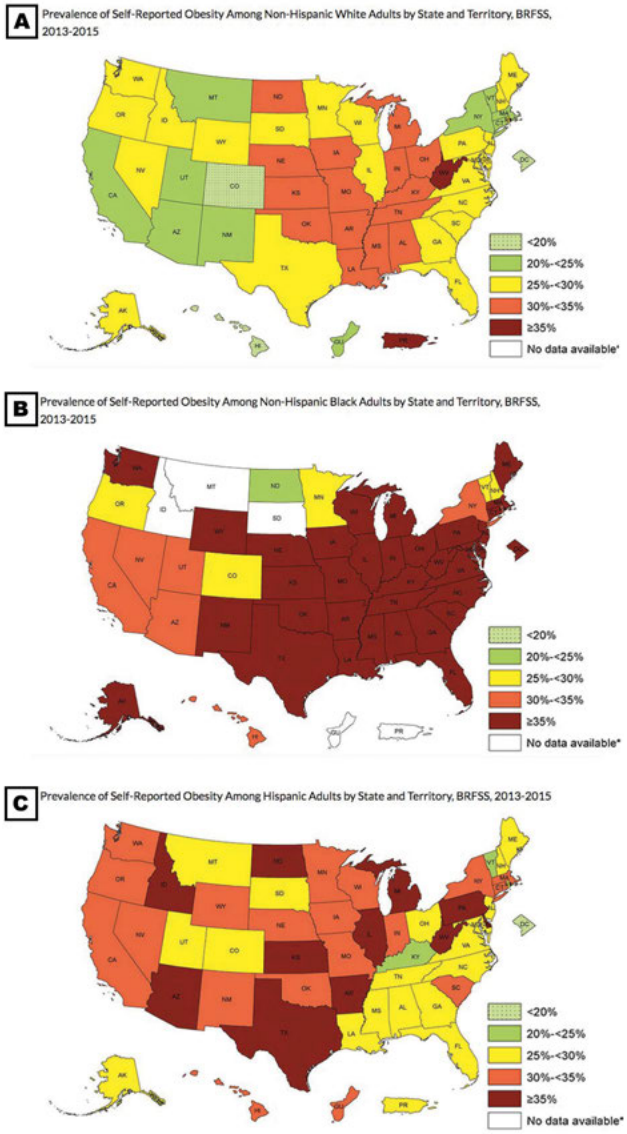

FIGURE 2: Self-Reported Obesity. CDC adult obesity prevalence maps[1] obtained from CDC website on August 10, 2017, and available online at https://www.cdc.gov/obesity/data/prevalence-maps.html. (A) Prevalence of self-reported obesity among non-Hispanic white adults by state and territory 2013–2015. (B) Prevalence of self-reported obesity among non-Hispanic black adults by state and territory 2013–2015. (C) Prevalence of self-reported obesity among Hispanic white adults by state and territory 2013–2015.

[1] CDC. Adult Obesity Prevalence Maps (2017). Available at: https://www.cdc.gov/obesity/data/prevalence-maps.html. (Accessed: 10th August 2017). Image in the public domain.

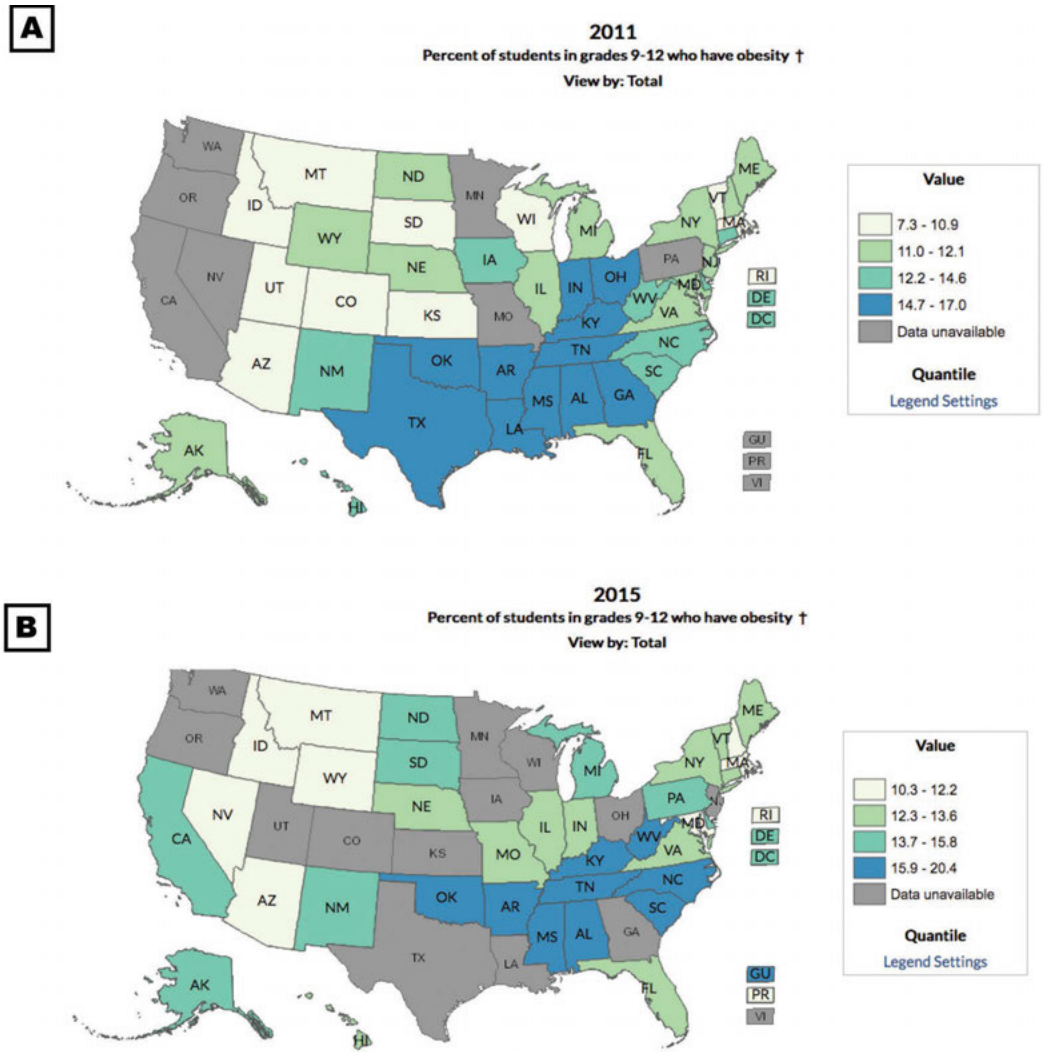

FIGURE 3: Obesity in Students in Grades 9–12. CDC Nutrition, Physical Activity, and Obesity: Data,Trends and Maps[2] obtained from CDC website on August 10, 2017 and available online at https://www.cdc.gov/nccdphp/dnpao/data-trends-maps/index.html. (A) Percent of students in grades 9 to 12 who have obesity by US states, 2011. (B) Percent of students in grades 9–12 who have obesity by U.S. states, 2015.

[2]CDC. Nutrition, Physical Activity, and Obesity: Data, Trends and Maps (2017). Available at: https://www.cdc.gov/nccdphp/dnpao/data-trends-maps/index.html. (Accessed: 10th August 2017). Image in the public domain.

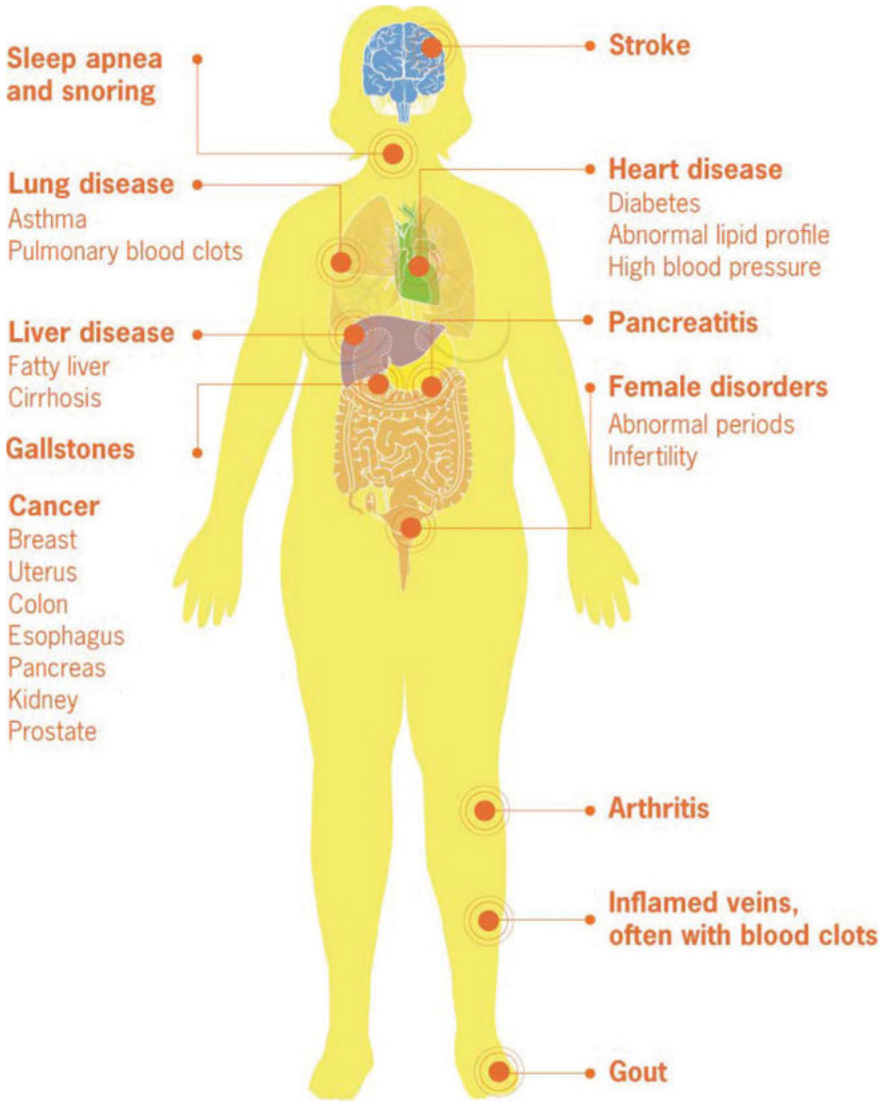

FIGURE 4: Obesity Complications. CDC Medical Complications of Obesity[3] obtained from CDC website on August 10, 2017, and available online at https://www.cdc.gov/vitalsigns/adultobesity/infographic.html

[3] CDC. Medical Complications of Obesity (2010). Available at: https://www.cdc.gov/vitalsigns/adultobesity/infographic.html. (Accessed: 10th August 2017). Image in the public domain.

of both diet and exercise is more likely to provide long-term benefit [24]; however, adherence to such lifestyle modifications is notoriously challenging. Given the high likelihood of weight re-gain, many dieters enter a vicious cycle of weight cycling or "yo-yo dieting" which increases risk of heart disease, stroke, and diabetes [25]. Thus, not only are lifestyle modifications largely ineffective, but repeated dieting and weight cycling imposes adverse health effects. A handful of pharmacologic agents have been developed to aid weight loss, but most have side effects and not all are approved for long-term use [26]. The effectiveness of obesity medications is typically modest, with most agents achieving 5% loss of body weight at 1 year [27, 28]. Although 5% weight loss can reduce risk of obesity-related complications, it is not enough to achieve a healthy body mass index (BMI) for most patients. Additionally, few studies have examined outcomes including potential weight regain after patients stop taking the medication, thus the long-term effectiveness of anti-obesity drugs is largely undetermined. Currently, the most effective obesity treatment is bariatric surgery, with the Roux-en-Y gastric bypass procedure (RYGB) producing an average loss of 5 BMI points at 5 years [29, 30]. In addition to substantial weight loss, bariatric surgery also alleviates obesity-related type 2 diabetes, hypertension, and joint pain [29], plus patients report increased quality of life after surgery [31]. The major drawbacks of bariatric surgery include the risk of complications and the cost which averages $15,000 to $25,000 [32, 33]. Because of this, surgery is usually reserved as a last resort for the morbidly obese (BMI, >40 kg/m^2), which comprise less than 10% of overweight or obese adults. Thus, moderately overweight or obese individuals who are still at risk for developing obesity-related complications have limited options for weight control (diet and exercise or pharmacotherapy), which provide only modest benefit. Therefore, there is a clear need to develop better strategies to promote weight loss and prevent weight gain to improve health outcomes for overweight and obese individuals.

It is also vital to understand why the surge in overweight and obesity has occurred, as this may suggest design of interventions to manage body weight. Average caloric intake has increased by around 240 kcals/day since 1970, with most of the increase attributed to carbohydrates [34]. Interestingly, fat intake decreased over the same period as obesity rates continued to rise, suggesting that excess caloric intake, not high dietary fat consumption, potentiates weight gain. Furthermore, occupational-associated energy expenditure has progressively declined since 1960 [35] and only 1 in 5 adults fulfills the recommend amount of daily physical activity [36]. Thus, one would speculate that the obesity epidemic is fueled by excess caloric intake combined with reduced physical activity, and hence disruptions to both arms of energy balance. Although this certainly explains what causes obesity, it does not explain *why* individuals overeat and move less. The increasing availability of palatable, calorie-rich, and inexpensive food has

fueled obesity rates [37], but what permits caloric intake in excess of metabolic demands? Under normal circumstances, energy intake is exquisitely coordinated with energy expenditure in an effort to defend body weight from both loss and gain [7, 15]. However, these mechanisms are not completely understood and are impacted by numerous variables (i.e., food palatability, genetics, sedentary lifestyle) that contribute to the development of obesity.

1.4 THE BRAIN COORDINATES ENERGY BALANCE

Energy balance strongly relies on behavioral output, namely, feeding and volitional activity that are controlled by the brain. Interestingly, most genes implicated in obesity have enriched expression in the nervous system [38], supporting the role of the brain as a master regulator of body weight. In particular, sub-regions of the hypothalamus have been implicated in regulating energy balance, including the arcuate nucleus (ARC), paraventricular nucleus (PVN), ventromedial hypothalamus (VMH) and the lateral hypothalamic area (LHA). The hypothalamus is found at the base of the brain near the third ventricle and is well positioned to intercept circulating energy cues from the periphery. Important hormonal cues detected by the hypothalamus include the anorectic hormone leptin and the orexigenic hormone ghrelin. Leptin is secreted from adipose cells as a signal of long-term energy storage and acts on hypothalamic nuclei to suppress food intake [39]. Ghrelin, by contrast, is secreted from the stomach as hunger increases and acts on the hypothalamus and other brain areas to promote food intake [40].

The ARC is a key site for energy integration and has been extensively studied in energy balance. The ARC contains two discrete neuronal populations expressing either agouti-related peptide (AgRP) or proopiomelanocortin (POMC), which exert opposing actions on feeding and body weight [41]. AgRP neurons are activated by physiologic hunger and promote food intake while reducing energy expenditure [42, 43]. AgRP neurons also express neuropeptide Y (NPY) and GABA, and the contribution of each individual neurotransmitter has been shown to increase feeding [44]. AgRP neurons are active in a fasted state, which is potentiated by ghrelin-mediated excitatory input [45, 46]. After a meal, ghrelin levels fall and leptin becomes a dominant circulating signal of energy status, which inhibits AgRP neurons to reduce food intake [47]. By contrast, neighboring POMC neurons are activated during satiation and suppress food intake while increasing energy expenditure [48–50]. POMC is a precursor protein that is cleaved into distinct fragments, including alpha melanocyte stimulating hormone (α-MSH), which exerts anorectic effects by binding the melanocortin-4 (MCR-4) receptors at key brain sites. Rodents deficient in MCR-4 signaling are hyperphagic and obese [51, 52] and MCR-4 mutations are the

most common monogenic cause of human obesity [53, 54], underscoring the importance of melanocortin signaling in energy balance. Although the ARC is a critical center for direct sensing of peripheral energy cues, POMC and AgRP neurons likely feed into a variety of downstream circuits that fine-tune feeding behavior and energy expenditure, such as the LHA. Indeed, POMC neurons project heavily to the LHA which expresses MCR-4 [55, 56], which may contribute to sympathetic regulation of glucose tolerance that can have beneficial effects for energy balance [57, 58]. However, the ARC and other mediobasal hypothalamic nuclei (e.g., the VMH and DMH) do not account for all central regulation of energy balance, and in particular do not explain how the brain coordinates the "motivated" feeding and moving behaviors that modify energy balance. This has led to the view that medial hypothalamic nuclei are primarily important for homeostatic feeding and energy expenditure, but that other hypothalamic sites might influence body weight via engaging the dopamine system that is well known to modify the motivation to eat and move [59].

1.5 DISCOVERY OF A ROLE FOR THE LATERAL HYPOTHALAMIC AREA (LHA) IN ENERGY BALANCE

The first study to suggest a function for the LHA resulted from an experimental accident, and serves as a reminder to let the data (not a preconceived hypothesis) lead understanding of the underlying physiology. Scientists had been studying animals with brain lesions in specific hypothalamic sub-regions, reasoning that the observed deficits in "lesioned" animals indicate what behavior and physiology is normally controlled via the site. Lesions within the ventromedial hypothalamus (VMH) caused striking overeating and subsequent development of obesity, and as a result of these experiments the VMH was declared a "satiety center" whose intact function is necessary for normal body weight (Figure 5). Anand and Brobeck sought to further define the VMH mechanisms that coordinate energy balance, so they generated a cohort of "VMH-lesioned" rats. They expected to observe the hyperphagia and obesity characterized in prior VMH lesion studies, but their experimental rats unexpectedly exhibited such severe, self-imposed aphagia that they died of starvation unless they were force-fed by the experimenters [60]. Subsequent examination of the brains from these rats revealed the source of the discrepancy: the lesions were not targeted to the VMH as intended, but instead were within the LHA. This serendipitous experiment promoted a view of LHA as the "feeding center" [60], thought to counteract the effects of the VMH "satiety center." LHA lesions were subsequently made in cats [61, 62] and monkeys [62] and produced similar feeding suppression as those made in rats. By contrast, electrical stimulation of the LHA increases feeding [61], exploratory behaviors,

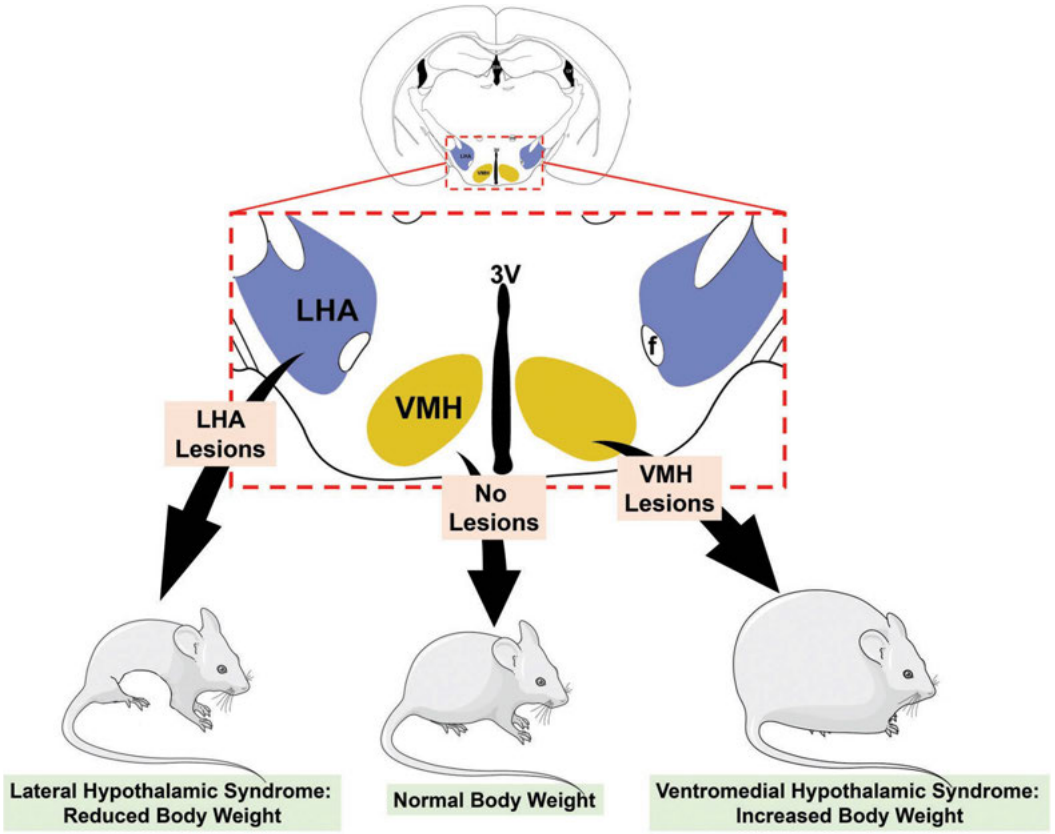

FIGURE 5: Impact of the VMH and LHA Lesions on Body Weight in Rodents. Coronal brain section as modified from the Paxinos and Franklin (2001) mouse brain atlas.[4] Rodent illustrations[5] were modified from Smart Servier Medical Art on October 24, 2017, available online at http://smart.servier.com/category/general-items/animals/

and intestinal motility in cats [63]. In rats, electrical stimulation of the LHA not only increased feeding but also the motivation to obtain food, determined by the rats willingness to press a lever and cross an electrical shock grid to obtain food [64]. Similarly, activating the LHA of goats triggered feeding and locomotion [65], which might reflect the fact that movement is necessary for these animals to procure food.

[4] Paxinos, G. & Franklin, B. *The Mouse Brain in Stereotaxic Coordinates* (Academic Press, 2001). Used with permission.
[5] Smart Servier Medical Art. Animals. (2017). Available at: http://smart.servier.com/category/general-items/animals/. (Accessed: 24th October 2017). CC-BY 3.0 license.

Taken together, the early lesion and activation studies were interpreted to support a "dual center hypothesis" in which the LHA and VMH exert antagonistic control of feeding. These descriptions are now recognized as oversimplifications, because the LHA and VMH are now accepted to contribute to many aspects of physiology beyond just feeding. Nonetheless, these loss and gain-of-function manipulations provided the first clue that specific hypothalamic subregions control strikingly different behaviors, and that there must be different, brain region-specific mechanisms to regulate feeding and energy balance.

1.6 "LATERAL HYPOTHALAMIC SYNDROME" SUGGESTS AN ESSENTIAL ROLE FOR THE LHA IN COORDINATING BEHAVIOR

The LHA was initially deemed a "feeding center" because animals with LHA lesions will not voluntarily consume food [66, 67]. Less emphasized, but equally important, is that LHA-lesioned animals also lose the motivation to drink water, and their resulting dehydration causes death well before starvation [66, 67]. However, rats with LHA lesions can be kept alive if they are administered food and water via stomach tubes [66–68]; this indicates that loss of action via the LHA impairs coordination of the need for resources and the motivation to ingest them, but it does not compromise the body's ability to utilize ingested resources. Intriguingly, the force-fed and force-hydrated LHA-lesioned rats termed as having "lateral hypothalamic syndrome" eventually recovered sufficient ingestive behavior to maintain survival via four distinct stages [67] reviewed below and in (Figure 6).

- Stage 1: LHA-lesioned rats exhibited total aphagia and adipsia, and their survival depended on experimenter-administered food and water via stomach tubes.
- Stage 2: Rats ate small amounts of moistened, palatable food, so were considered to exhibit anorexia as opposed to aphagia. Rats remained adipsic and required experimenter-administered fluids.
- Stage 3: Rats voluntarily consumed some dry food as long as they were kept hydrated and would eat enough moistened palatable foods to support regulation of body weight without experimenter-administered nutrition. However, rats still did not voluntarily drink water.
- Stage 4: Rats were considered "recovered" because they accepted dry food and drank water, thus they no longer required force feeding/hydration to live. The recovered animals maintained sufficient body weight for survival, but their weight was lower compared with those with intact LHA action [67, 69, 70].

Stage	Defining Characteristic	Wet Palatable Food Consumption	Regulation of Body Weight and Food Intake on Wet Palatable Food	Dry Food Consumption with Hydration	Water Consumption. Survival with Water and Dry Food Intake.
1	Adipsia, Aphagia	✗	✗	✗	✗
2	Adipsia, Anorexia	✓	✗	✗	✗
3	Adipsia, Dehydration Aphagia	✓	✓	✓	✗
4	Recovery	✓	✓	✓	✓

FIGURE 6: Lateral Hypothalamic Syndrome. Hallmarks of the lateral hypothalamic syndrome stages.[6] Modified from Teitelbaum, P. & Epstein, A. N. (1962). The lateral hypothalamic syndrome: recovery of feeding and drinking after lateral hypothalamic lesions. *Psychological Review* 69(2), 74–90.

These data suggested that the LHA is important for energy *and* fluid balance, but that other brain sites can, in time, sufficiently regulate ingestive behavior to permit survival. However, upon careful study, even the rats that had "recovered" from lateral hypothalamic syndrome remained unable to appropriately respond to altered energy or fluid status with appropriate intake behavior. For example, normal rats respond to peripheral cues of insufficient energy status (e.g., low blood sugar or fasting) by eating more food, but the recovered lateral hypothalamic rats did not adjust feeding in response to these stimuli [71]. Likewise, recovered lateral hypothalamic rats did not counter dehydration with increased drinking behavior, and in fact only exhibited prandial drinking (e.g., water intake to facilitate chewing and swallowing of food) [67, 72, 73]. Similarly, they did not respond to dipsogenic stimuli (i.e., thirst-inducing treatments such as hypertonic saline or polyethylene glycol) with appropriate drinking behavior, and hence also exhibited abnormal urinary water output [74, 75, 76]. Fascinatingly, if these rats had the choice of receiving water through stomach tubes or the mouth they preferred it via the stomach [77], suggesting a pervasive, diminished motivation to voluntarily drink. The phenotype of lateral hypothalamic syndrome was similar in young and adult rats [78, 79], but recovery was impaired in

[6] Teitelbaum, P. & Epstein, A. N. The lateral hypothalamic syndrome: recovery of feeding and drinking after lateral hypothalamic lesions. *Psychol. Rev.* 69, 74–90 (1962). Used with permission of the American Psychological Association (APA).

juvenile rats compared with adults, emphasizing the importance of an intact LHA for development and survival [78, 80]

At face value, these data suggest that the LHA is important for the *physiologic motivation* to consume. However, perhaps, a more parsimonious interpretation is that the LHA is necessary to coordinate changes in metabolic and fluid status with appropriate ingestive behavior to resolve them. This also makes the LHA unique from other mediobasal hypothalamic sites with documented roles in energy balance, but not for fluid intake. Thus, the LHA is distinctive because it adaptively modifies both ingestive behaviors necessary for homeostasis and survival.

1.7 PHYSIOLOGIC AND PHARMACOLOGIC REGULATION OF THE LHA

Experimental lesions and electrical stimulation implicated the LHA in motivated ingestive behavior, but the activity of LHA neurons is also regulated by endogenous and exogenous stimuli relevant to maintaining energy and fluid balance. For example, early studies hinted that the LHA might modify peripheral glycemic control in response to alterations in plasma insulin and glucagon levels [81, 82]. Indeed, central treatment with glucose [83, 84], free fatty acids [85], and insulin [84] does modify the activity of some LHA neurons. These peripheral cues convey ample energy status to the brain, and presumably, the LHA detects these signals and modifies output ingestive behavior accordingly. Moreover, the LHA was also implicated in coordinating the motivation to obtain food, including willingness to work for it. Surveillance of LHA neurons in monkeys shows that their activity changes during a lever pressing-task to obtain food [86]. These data suggest that some LHA neurons are regulated as part of the process of harmonizing resource need and behavior. Indeed, electrical stimulation of the LHA increases rats' motivation to learn, which mimics the impact of food deprivation upon neural activity [87]. Consistent with a role for the LHA in water intake, osmolality changes are also detected within the LHA [83, 88], and may serve to couple thirst with drinking behavior needed to resolve it. Intriguingly, pharmacological data suggest that feeding and drinking might be regulated via ligands acting upon distinct subsets of LHA neurons. For example, administration of adrenergic reagents into the LHA of sated rats induces feeding [89, 90], whereas the injection of a cholinergic reagent into the LHA resulted in drinking behavior [89, 90]. Cholinergic reagents also trigger drinking when injected into the preoptic area [91] and lateral septal nucleus [92], but fail to do so if administered to recovered LHA-lesioned rats. These data suggest that LHA-mediated control of drinking in the LHA occurs via a distinct mechanism compared with that via other brain areas.

1.8 NEURONAL DIVERSITY IN THE LHA AND IMPLICATIONS FOR ENERGY BALANCE

Initial studies of the LHA manipulated the entire region, but such bulk regulation is unlikely to occur physiologically because of the cellular heterogeneity of this region. Indeed, it is now recognized that the LHA contains many molecularly distinct populations of neurons, which are differentially implicated in control of feeding, drinking, locomotor activity, goal-directed behaviors, sleep/arousal or responses to stress or inflammation [93–103]. As a result of these findings, the early designation of the LHA as a "feeding center" has fallen out of favor because it vastly under-represents the myriad ways in which the LHA can modify behavior to contribute to energy and fluid homeostasis. However, the molecular phenotyping of subsets of LHA neurons has enabled development of genetic methods to specifically identify LHA populations and study their contributions to physiology. Subsets of LHA neurons also receive information concerning energy status that may be important for appropriately coordinating feeding and other motivated behaviors. Some LHA neurons express receptors for the orexigenic hormone ghrelin [104, 105], whereas separate LHA neurons express receptors for the feeding suppressing hormone leptin [106, 107], indicating that the LHA directly intercepts circulating cues with opposing results upon energy balance. The LHA also receives dense input from the ARC [55], and thereby receives indirect information regarding peripheral energy status. Taken together, this work suggests that the LHA is uniquely positioned to integrate specific peripheral energy cues with appropriate motivated behaviors to adapt resource intake. Given that the LHA responds to anorectic, orexigenic and dipsogenic cues, there are likely distinct neural mechanisms by which the LHA can coordinate motivated behaviors and homeostasis. Indeed, several populations of neurons have been described in the LHA that vary in neurotransmitter and neuropeptide content, projection targets and function. The connectivity of key LHA neuronal populations will be discussed in Chapter 2, and Chapters 3 to 5 will provide the current understanding of how these LHA neurons contribute to feeding, drinking and movement behaviors related to energy balance. Similar to the underlying premise of lesion studies, understanding how disruption of specific LHA populations or pathways compromises homeostasis will inherently reveal how they coordinate normal physiology. These findings may suggest the development of novel strategies to promote weight loss and maintenance of healthy body weight necessary to overcome the obesity epidemic.

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