Obesity: Peripheral Signals, Neural and Peptidergic

129

Ilia N. Karatsoreos and James H. Peters

Contents

Abstract

Obesity is a global public health problem linked to increased risk for many disorders including diabetes, cardiovascular disease, and even cancer. The World Health Organization estimates almost 2 billion adults worldwide are considered overweight with nearly 600 million of those individuals also being

I. N. Karatsoreos (✉)
Department of Psychological and Brain Sciences, University of Massachusetts Amherst, Amherst, MA, USA
e-mail: ikaratsoreos@umass.edu

J. H. Peters
Department of Integrative Physiology and Neuroscience, Washington State University, Pullman, WA, USA
e-mail: James_peters@wsu.edu

D. W. Pfaff et al. (eds.), *Neuroscience in the 21st Century*,
https://doi.org/10.1007/978-3-030-88832-9_155

considered obese. How did we get here? The laws of thermodynamics would suggest it is simply a fact that we consume too many calories without burning an equal number, thus causing an imbalance that results in weight gain and eventual obesity. Such a situation would thus be easy to address, since simply reducing caloric intake would eliminate the problem. However, the story is far more complex and involves the interplay between both central and peripheral systems that regulate energy metabolism, energy consumption, and even the brain's reward circuitry. This chapter explores the peripheral signals that not only contribute to obesity but also make it difficult for us to break the cycle that leads to metabolic dysregulation and obesity. We will specifically consider obesity in the context of the brain, which coordinates feeding, activity, circadian rhythms, and metabolic functions, while also being a target for many metabolic hormones. Thus, the state of being obese leads to changes not only in the periphery but also centrally within the brain. How this affects brain structure and function will also be discussed.

Keywords

Metabolic syndrome · Hypothalamus · Brain stem · Circadian rhythms · Corticosterone · Cortisol · Glucocorticoids · Insulin · Glucose · Leptin · Endocannabinoids · Reward · Gastrointestinal · Liver · Pancreas · Stomach · Vagus

History and Context

Obesity is a global public health problem that results in an increased risk for diabetes, heart disease, cancer, and other illnesses. According to the World Health Organization (WHO), more than 1.9 billion adults worldwide are considered overweight, with 600 million of these individuals being considered "obese." This means that approximately 13% of adults worldwide are obese and results in a staggering statistic: Most of the world's population lives in nations where the negative health effects of being obese kill more people than the negative health effects of being underweight. The effects on children are perhaps starker, with WHO estimating that 38 million children under the age of 5 were considered overweight or obese in 2019. This demonstrates that metabolic disorders and obesity are not restricted to the developed world and not restricted to a single age group. With the acceleration of rates of global obesity and relatively few effective treatment options, it is imperative that new treatment strategies are devised. However, gaps in our understanding of body weight control, particularly when individuals start down the road to metabolic dysregulation and obesity, continue to hamper progress toward this goal (Fig. 1).

Perhaps one method to accelerate the development of innovative treatments for obesity is to accept the realization that obesity is largely a "brain disorder." Thus, it is important to highlight that the brain has a central role in the development of obesity while also being affected *by* obesity. As such, the brain and periphery are both

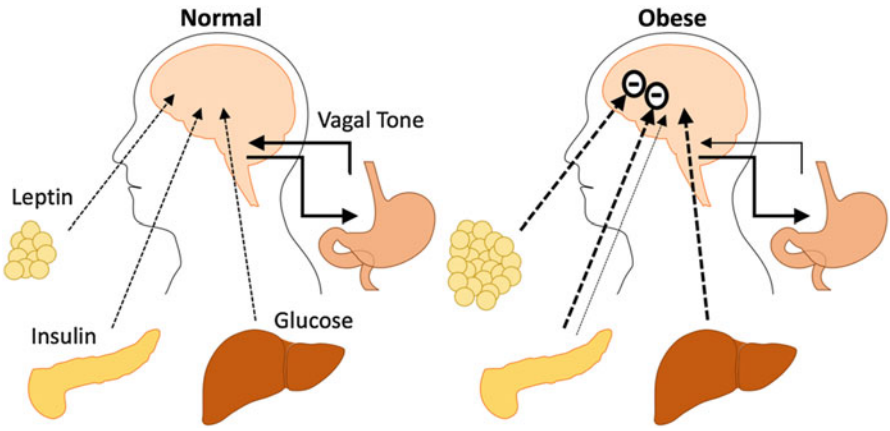

Fig. 1 Peripheral signals in obesity can drive changes in the brain. Under normal conditions (left), peripheral signals from a number of organs such as leptin from white adipose tissue, insulin from the pancreas, glucose from the liver and bloodstream, and signaling through the vagus nerve help to balance central systems regulating appetite, feeding, and metabolism. However, dysregulation of these signals can lead to development of the metabolic syndrome and the obese phenotype. Under the obese phenotype (right), these same signals fall out of balance. While leptin from adipose may greatly increase, central leptin sensitivity is reduced. Similarly, increased insulin at early stages of obesity can lead to development of insulin resistance in the brain and periphery and eventually full-blown type 2 diabetes with gradual decrease of insulin output from the pancreas. Glucose homeostasis in the liver can also be disrupted, which then affects glucose sensing centrally. Vagal tone is significantly lower in the obese phenotype, thus disrupting sympatho-vagal regulation of the periphery (Sartor 2013). This provides a further disruption to the delicate balance that normally maintains control over appetite, feeding, and metabolic processes

components of the "two-way street" of obesity. Therefore, exploring periphery-to-brain mechanisms that contribute to the development of obesity, and the effects of obesity on central nervous system function, will offer creative and likely transformative translational approaches to this global problem.

This chapter delineates neural mechanisms of normal physiological processes controlling food intake and metabolism which, when perturbed, translate in time to the development of pathophysiological obesity and metabolic disorders. In addition, we will discuss the growing evidence that peripheral metabolic signals drive changes within the central nervous system, thereby compounding the dysregulation of central feeding circuits. Overall, we present obesity and metabolic syndrome in the context of the brain–body interactions, a perspective that has become a central tenet in neuroscience.

Progressing from the Nonobese to the Obese Phenotype

Fundamentally, obesity is caused by excess caloric consumption with insufficient caloric utilization. This "calories in, calories out" rule of thumb, though useful,

oversimplifies the situation and says nothing about the mechanisms by which such an imbalance can arise. Because of the large and rapid increase in global prevalence of obesity, it is tempting to attribute it a major dysregulation of the normal control of feeding and metabolic physiology. Environmental considerations (including increased access to high-calorie foods and decreased exercise) are certainly part of the etiology of obesity. However, given our increased understanding of the mechanisms that guide the precise control of food intake (determined by the reciprocal peripheral to central signaling), we now better appreciate the development of obesity as the cumulative effect of subtle mismatches in caloric intake and expenditure. For example, depending on the context, caloric intake discrepancies as small as 0.5% will incrementally result in excess weight gain. Given this perspective, understanding the peripheral neural and hormonal signals informing central nervous system (CNS) control of food intake, metabolic output, and the constant balancing of these processes becomes of central importance.

The development of obesity entails the progression of relatively normal physiological processes over time given an "obesogenic" environment to the clinical end points of the overweight and obese phenotypes. This requires understanding the peripheral signaling under normal circumstances while anticipating the dysregulation once clinically relevant pathophysiology is reached. To begin, it is necessary to clarify definitions of these clinical end points.

Overweight Versus Obese

According to national and international public health bodies, including the WHO, the classification of overweight and obese is defined broadly as an abnormal or excessive accumulation of white adipose tissue (fat) that is a risk to health. In terms of body mass index (BMI), the specific definition of an "overweight" individual is a BMI of 25 or higher, while an individual is considered "obese" when BMI exceeds 30. BMI should be considered a guide and does not necessarily correspond to the same level of adipose tissue across individuals (www.who.int).

Metabolic Syndrome

While many use the terms obesity and metabolic syndrome interchangeably, metabolic syndrome is a clinically defined cluster of conditions, of which excess body fat (particularly around the waist) is one symptom. In clinical practice, metabolic syndrome is defined by at least three of the following: excess body fat around the waist, high blood sugar, elevated blood pressure, and high plasma cholesterol levels. This clustering of symptoms which define metabolic syndrome, when left untreated, results in increased risk of serious chronic diseases including cardiovascular disease and type 2 diabetes. It is possible for an obese individual to not have metabolic syndrome and an individual with metabolic syndrome to not be obese; however, both of these outcomes are highly unlikely, as the conditions are intimately linked on the physiological level.

It is important to note that such conditions do not develop rapidly but usually progress over months and years. In addition, these conditions do not always present in a comorbid fashion, though presenting the full complement of these symptoms comprises a serious health risk. In part, because of the insidious nature of many of these symptoms, it is difficult for many individuals to fully appreciate the gathering metabolic storm, making prevention and treatment excessively difficult. In the context of this chapter, this panoply of symptoms appears mostly "peripheral" in nature, thus divorcing brain mechanisms from these effects. Our goal in this chapter is to highlight that many of these changes are a result of a dysregulation between periphery-to-brain communication, causing central responses that are ineffective in – or even counterproductive to – regaining normal control over body weight. But how is body weight actually maintained?

First, it is important to clarify which are the regulated physiological processes that impact the obese phenotype. Very often, weight (or perhaps mass of white adipose tissue) is considered the regulated parameter; however, this does not appear to be the case in most instances. Instead, the regulated parameters are the feeding and metabolic systems that primarily control food intake, circulating fuels, and metabolic output. Thus, though tissues such as adipose can directly inform central feeding circuits by way of neural and hormonal signals, they are not the physiological variable being regulated. We will now briefly describe central circuits that monitor and regulate these critical regulated parameters.

Primary Circuits in the CNS Controlling Feeding

Brainstem Circuits

The overweight and obese conditions in most cases arise over long periods of time with the progressive accumulation of fat. This fundamentally reflects an imbalance in the amount of calories consumed versus the energy utilized for metabolic needs. While the obese phenotype can be striking, the imbalance in caloric intake only needs to be slightly higher than the metabolic demand to create the physiological environment for adipose accumulation. The body is charged with matching continuous and variable metabolic demands with only episodic food intake. To ensure uninhibited access to energy, the adaptive natural condition is to preferentially store excess energy in anticipation of lean times when food is not so plentiful. As such, it is relatively easy to acquire fat tissue and exceedingly difficult to get rid of it. It is assumed that this adipose accumulation occurs at a fairly constant rate throughout the life span reflecting a chronic imbalance in registering intake. However, periodic episodes of large amounts of food intake (celebrations or holidays) may disrupt otherwise well-balanced consumption (Turicchi et al. 2020). In either case, the physiological controls of both food intake and metabolic demand inform our understanding of the underlying physiological problem(s). Primarily, is there an ongoing problem or is it periodic? In this section, we will detail the primary and secondary controls of episodic food intake and explore how they change in the obese condition.

Primary Controls of Food Intake

Ingestion of food is arguably one of the most important behaviors performed and potentially one of the most dangerous. As a consequence, the body possesses robust neural innervation of the alimentary canal to monitor and control both the type and amount of food ingested. A fundamental principle of this monitoring is that it occurs largely prior to any absorption of the food. This allows for the expulsion of potentially dangerous foods as well as the appropriate pacing of intake and transit through the gastrointestinal tract to maximize nutrient absorption. This begins at the level of the oral cavity (mouth). The oral cavity is innervated by the facial (7th) and glossopharyngeal (9th) cranial nerves, with the afferent component of these nerves conveying the "taste" of the food to brainstem. The coherent "taste" information reflects multiple qualities of the food including temperature, texture, primary flavors (salty, sweet, sour, bitter, and umami), and aromatic bouquet (smell). This perception of the food is exceptionally accurate at predicting the specific nutrient content including the amount and component nutrients such as the relative contributions of carbohydrates (both complex and simple), fat, and protein. This sensory information is important to coordinate the motor reflexes necessary for chewing and swallowing as well as initiating "cephalic" phase reflexes from the gastrointestinal tract. These include increased insulin secretion proportional to the perceived sugar content and increased secretion of digestive enzymes (Giduck et al. 1987).

Throughout a meal, the relative palatability of food decreases. This is due in large part to neural feedback from the gastrointestinal tract conveying the amount and nutrient content of the ingested food. This is best illustrated by the fact that normal feeding is rapid initially and then decreases through the meal. In addition, food selection shifts from the least palatable to most palatable throughout the meal reflecting the relative change in palatability. It is not an accident that dessert occurs at the end of the meal!

In obese individuals, the sensitivity to oral sensory processing is diminished (Berthoud and Zheng 2012). This likely occurs via multiple mechanisms including desensitization of the cognate receptors in the primary afferent neurons. As a consequence, the relative palatability of food is diminished. This might suggest a decrease in total food intake, but what typically happens is a shift in food selection to more highly palatable foods, specifically those high in refined sugar and saturated fats. This decrease in sensitivity can also disrupt cephalic phase reflexes including anticipatory insulin secretion, thus contributing to poorer blood sugar control.

Gastrointestinal Feedback Via Primary Vagal Afferent Neurons

Normal controls of food intake are primarily defined around the unit of the meal. The transition from initiating a meal-to-meal termination with the intervening physiological responses constitutes a coherent unit of control for episodic eaters like humans. The coordination of this process and the development of satiety are largely controlled by the vagal innervation of the upper gastrointestinal tract (Ritter 2004).

Primary satiation and meal termination are largely determined via the upper GI prior to very little absorption having occurred. The process of satiation controls the transit of food through the upper gastrointestinal tract and serves to optimize digestion and absorption.

Information about the amount and type of food in the upper gastrointestinal tract is conveyed to the brain via the vagus nerve (10th cranial nerve). The vagus is composed predominantly of afferent fibers (~70%) with a minority of motor neurons. The afferent fibers are highly heterogeneous but can be broadly divided based on their degree of myelination, which corresponds to their modality of activation. Specifically, the physical distension and stretch of the stomach is generally conveyed to the brain via activation of large-diameter-myelinated A-fibers, whereas small unmyelinated C-fibers relay chemical and nutrient-derived signals. While this partitioning of information is only approximate and not a strict segregation, it does reflect the fact that different qualities of information necessitate distinct physiological responses. In addition, they are also not of equivalent importance in their control of food intake. The activation of C-fiber afferents is far more salient in initiating the process of satiety than A-fibers.

Following swallowing, food enters the stomach where mechanical and enzymatic digestion continues. The initial bolus of food quickly transits into the duodenum where it stimulates the release of multiple chemicals including cholecystokinin (CCK). This initial release of CCK directly activates primary vagal afferent neurons to promote pyloric constriction, which decreases gastric emptying and increases gastric activity. This feedback ensures that nutrient transit is slowed out of the stomach in order to maximize absorption in the small intestine. CCK is just one of many paracrine/endocrine signals released from the gut which act on the vagal afferent neural innervation. Other secreted signals in the upper gastrointestinal tract include ghrelin, leptin, gastrin, secretin, gastric inhibitory peptide (GIP), and glucagon-like peptide-1 (GLP1). Each of these chemicals has high-affinity receptors in multiple tissues of the gastrointestinal tract as well as in the vagal afferent neurons. As a result, they both mediate local digestive functions (such as exocrine/endocrine secretion) as well as convey key information to the brain.

In addition to the within-meal controls, the body conveys ongoing fuel stores and metabolic demands with direct impact on these controls of food intake. This is particularly apparent in glucoprivic feeding wherein the perception of diminished blood sugars necessary to fuel the brain results in ravenous hunger and severely altered satiety cues (glucose is further discussed below, and adeptly reviewed in Ritter et al. 2019). Similar in principle, other circulating nutrients such as fatty acids or hormones reflective of nutrient status, such as leptin, can significantly alter the normal satiety cues originating from the gut. This occurs in large part through direct action on the vagal afferent neurons and neurons contained in the nucleus of the solitary tract (NTS). Lastly, the recent increase in bariatric surgery has revealed an intimate connection between vagal afferent signaling in the upper gastrointestinal tract and prevalence of metabolic syndrome and type 2 diabetes.

In overweight and obese individuals, there is a primary decrease in the generation and perception of normal satiety signals. The best studied of these is the diminished

ability of CCK to promote vagally mediated satiety. This is thought to be a result of high-fat diets either decreasing CCK secretion, decreasing the expression of CCK receptors, or both. The net effect is that normal caloric and nutrient loads are insufficient to satisfy the drive to eat, and so larger meals are consumed. Even small changes in these processes can result in cumulative weight gain over time.

Secondary Integration of Oral, Gastrointestinal, and Humoral Food-Related Signals

A major role for the CNS is to match episodic food intake with energy storage and continuously variable energetic demands, mismatches of which result in increased fat mass and the development of obesity. The neural circuitry contained in the brainstem is in itself sufficient to produce satiation and provide coherent control over food intake independent of higher-order processing (Grill and Hayes 2012). Analysis of the fundamental units of ingestion suggests these reflexes/behaviors do not require forebrain structures to occur and speak to the fundamental importance of these circuits in controlling food intake and digestion. While remarkable, the primacy of this ancient circuitry likely contributes substantially to the general inability to clinically intervene in the treatment of obesity.

Neural signals arising from afferent innervation of the oral cavity and upper gastrointestinal tract contact the brain in the nucleus of the solitary tract (NTS) in the brainstem. This convergence of the facial, glossopharyngeal, and vagal afferent neurons provides the first point of integration and processing of these signals. This area of the brain also has a very permeable vasculature allowing for the relatively easy passage of circulating factors to influence the neural signals. Anatomically, the NTS resides in the dorsal aspect of the medulla and forms a Y (or straddles) around the caudal fourth ventricle. The NTS is also immediately under and continuous with the area postrema (AP), another key nucleus in the control of food intake, in particular in the production of nausea and vomiting. Just ventral to the NTS is the dorsal motor nucleus of the vagus (DMV), which contains the cell bodies of the preganglionic vagal motor neurons.

Neurons intrinsic to the NTS mostly contain glutamate as their fast neurotransmitter; however, there exist sizable inhibitory populations that use GABA as their fast neurotransmitter. Nearly every specific receptor subtype for both glutamate and GABA are present in the afferents and the NTS neurons including AMPA/Kainate, NMDA, mGLURs, GABA A, and GABA B. In addition, neuropeptide receptors, including oxytocin, vasopressin, melanocortins, leptin, CCK, GLP, and insulin, are expressed either in the afferent terminals or on NTS neurons resulting in a near recapitulation of the ability to perceive peripheral gut peptides centrally (Grill and Hayes 2012). Peptides are largely suspected to mediate the descending controls of the NTS function from forebrain structures such as the hypothalamus; these include the melanocortins, oxytocin, and vasopressin. Lastly, many other neurotransmitters such as serotonin, acetylcholine, dopamine, and epinephrine/norepinephrine also have cognate receptors in the NTS and provide for layered and complex control over

the processing and outputs of this first central nucleus. As such, while the primary afferents drive the initiation of circuit function, the NTS is well equipped to integrate multiple levels of central and peripheral information to produce coherent response. Below, we simplify our consideration of this processing to the afferents and the flow of information either back to the periphery or to the forebrain.

Neurons intrinsic to the NTS overwhelmingly receive primary afferent innervation. These afferent contacts control meal size and reflex function through strong excitatory glutamatergic synaptic connections. The segregation of afferent function/modality (A- vs. C-fibers) in the periphery is maintained at this first level of processing in the brain. There are typically pronounced differences in the relative weight (strength) between C- and A-fiber-mediated reflexes. Information received via the NTS that stays local (brainstem) has simple circuitry, while information forwarded to other brain regions has more processing (Andresen et al. 2004). NTS-mediated reflex pathways control gastric emptying, GI secretion/motility, and redistribution of blood flow during ingestion. In the simplest pathway, this involves primary afferent to NTS to DMV to the effector organ. In contrast, NTS pathways culminating in projections to forebrain targets often receive polysynaptic innervation from the primary afferents, which can be either inhibitory or excitatory. Processing in higher-order neurons in the NTS also integrates A/C fiber information. This is commonly seen as primary afferent-driven inhibitory inputs (GABA) on to projection neurons. The net effect of this circuit is the ability to amplify and diminish the output of forebrain-projecting neurons from the NTS. These modifications are often neurally generated but can also reflect the energetic and hormonal environment in the nucleus. For example, circulating metabolic hormones including leptin and insulin manifest their impact on autonomic output and feeding in part via their control over neural processing in the NTS.

While much is known about the brainstem controls of food intake and autonomic function, including the contribution of the NTS, we are only beginning to understand how obesity impacts this neural circuitry. These changes can be a result of maladaptive changes intrinsic to the nervous system or reflective of the circulating metabolic and hormonal environment. Below are listed some of the more common phenotypes:

1. *Autonomic dystonia.* Decreased heart rate variability. This symptom results from changes occurring at multiple levels of the circuit resulting in the imbalance between the sympathetic and parasympathetic innervation of the heart and very likely other organ systems. It is a major predictor for poor health outcomes over the life span.
2. *Poor satiety efficacy.* Chronic high-fat diets and the progression of obesity lead to decreased GI efficiency and dysregulated absorption and function. These outcomes are a result of changes intrinsic to the nervous system as well as due to circulating factors.
3. *Decrease in sensitivity to normal food-related cues*. As detailed above, the progression of obesity portends the general decrease in sensitivity to oral and gastrointestinal signals to the brain. This process is a major point for neural/humoral interactions.

4. *Decreases in the descending control of brainstem function.* The hypothalamus provides gain control over the NTS neural circuits and relays, in part, the influence of circulating hormonal factors such as leptin. The development of obesity results in an overall diminishment of this control via multiple mechanisms including leptin resistance.

Overall, the conveyance of peripheral signals, both oral and gastrointestinal, are essential for the normal controls of food intake and energy metabolism. The circuitry contained within the brainstem including the NTS produces coherent autonomic and physiological responses, disruption of which can result in serious health concerns and further the pathophysiological sequelae associated with overweight and obese phenotypes.

Obesity as a Disorder of Body–Brain Communication: The Hypothalamus and the Neuroendocrine Connection

Tremendous resources have been focused on understanding the physiological causes and consequences of obesity. The recognition of the CNS as the major conductor in orchestrating the neural and humoral control of food intake and metabolism is thus a crucial starting point to fully unraveling the mechanisms of these metabolic changes. Viewing the experimental and clinical findings through the lens of the nervous system can thus provide an important perspective to both basic scientific understanding and clinical intervention.

In this context, it is useful to consider this reciprocal communication system as a form of neuroendocrine signaling. The number of unique molecules with origins in the periphery that have been discovered to alter metabolic function and energy balance has increased exponentially, with nearly 100 identified to date. This section focuses on four of these molecules: glucose, insulin, leptin, and cortisol. These molecules were chosen because they have both peripheral and central effects, they have clear influences on both hunger and satiety, and significant work has been undertaken to determine the molecular mechanisms by which they alter function in both the periphery and CNS.

As has been discussed elsewhere in this text, the discovery of hypothalamic control of feeding has a long history (Gao and Horvath 2007). In the 1950s, several groups started to contribute to a theory of hunger and satiety that focused on the hypothalamus, specifically on two hypothalamic regions, the ventromedial hypothalamus (VMH) and the ventrolateral hypothalamus (VLH). This model was based on data that showed destruction of the VMH led to hyperphagia, while VLH lesions would lead to hypophagia. Thus, the "dual center hypothesis" suggested that the VMH was the satiety center, while the VLH was the hunger center. While a useful model, it rapidly became clear that the complete story was far more complex. For example, rather than eating until they burst, or wasting completely away, leaving VMH- and VLH-lesioned animals to their own devices for longer periods of time displayed a quite unexpected change in behavior and physiology. Specifically,

VMH-lesioned animals reached a new higher body weight and ate the appropriate amount of food to maintain this higher body weight, while VLH-lesioned animals reached a new lower body weight and consumed only enough food to maintain this new standard. Clearly, then, other factors were involved in the maintenance of body weight, and the neural circuits involved were more nuanced and extensive than just these two regions. Over the intervening decades, the circuitry for the feeding–metabolism circuit has been more fully elucidated. This includes a better understanding of the role of humoral signals from the periphery, the involvement of the vagus nerve, and brainstem feeding circuits and their interactions, in feeding behaviors. While the goal of this chapter is not to fully outline these circuits, the remainder of this section discusses the mechanisms by which peripheral signals gain access to central feeding centers and focus on the role of neuroendocrine and hormonal feedback to both the brainstem and hypothalamic feeding centers.

The hypothalamic feeding circuits contribute to the regulation of the timing and motivation of feeding and food-related behaviors. These circuits are also exquisitely sensitive to both neural and humoral feedback from the periphery to further shape feeding behavior (discussed later in this chapter). In addition, new data are emerging that indicate marked synaptic plasticity in the hypothalamus in both human and animal models of obesity, including changes in glial cells and neuron–glia interactions. The hypothalamus has been a major focus of research on obesity, as this brain area contains numerous interacting systems that regulate feeding, satiety, and other motivational states. It is also the region containing the SCN master circadian clock and the paraventricular nucleus (PVN), a central node in the hypothalamic–pituitary–adrenal (HPA) axis that regulates glucocorticoid secretion. In addition, the hypothalamus contains key neurons that oversee the regulation of energy homeostasis (i.e., the precise matching of caloric intake with energy expended that normally keeps body weight relatively stable over many years).

One way the hypothalamus regulates energy consumption is by its ability to sense the nutrient glucose, an essential molecule for energy production in the cell. Glucose-sensing neurons (cells that alter their firing in response to changes in extracellular glucose concentration) were first discovered in the 1960s. These directly glucose-sensitive cells, located in the ventromedial hypothalamus, the lateral hypothalamic area, and the arcuate nucleus of the hypothalamus, show both increases and decreases in firing in response to elevations of glucose in the extracellular compartment. This change in firing is then known to drive changes in several consumatory behaviors through both hormonal and neural mechanisms to alter both food intake and metabolic output. Thus, the hypothalamus may be a central nexus, the complex interaction with other critical brain areas such as the brainstem (discussed below), which is critical in the detection of circulating glucose. This collaboration between brain areas provides for the coordination of a neurobehavioral response to ensure adequate supply of glucose by changing feeding behaviors and metabolic processes such as body temperature and locomotor activity.

Glucose is obtained from food and taken up by cells and used for energy production via the glycolytic pathway. This pathway metabolizes a single molecule of glucose into two molecules of pyruvate and two molecules of adenosine

triphosphate (ATP), which is the energy currency of cells. In addition to glucose that is immediately utilized, much of the circulating glucose is converted to glycogen for longer-term storage, primarily by the liver. However, cells cannot store large quantities of glycogen due to it being very hydrophilic and disrupting osmotic pressure inside the cell. Therefore, when there is excess carbohydrate in the cell, it is catabolized into acetyl-CoA, one of the primary inputs to the fatty acid synthesis pathway, and hence promotes formation of triglycerides and lipids for long-term storage. Thus, regulation of glucose in the blood stream is crucial. Glucose sensing in the CNS has significant impacts on peripheral function via connections through the brain stem and the autonomic nervous system, such as the rostral ventrolateral medulla and the caudal ventrolateral medulla. However, the hypothalamus is a major target of glucose as well. As described above, glucose-sensing neurons are found in many hypothalamic areas, including the dorsomedial hypothalamus, paraventricular nucleus, ventromedial hypothalamus, lateral hypothalamic area, and the arcuate nucleus. These centrally mediated processes then help to drive changes in feeding behavior and metabolism to ensure a constant supply of energy. Thus, this peripherally derived signal can directly impact function of the CNS, which then drives changes in behavior and peripheral function. But glucose is not the only peripherally derived signal that can have effects on the brain.

When glucose is extracted from food consumed by the organism and enters the bloodstream, the peptide hormone insulin (produced and released by beta-cells of the pancreas) is released. Insulin stimulates the uptake of glucose from the blood by skeletal muscle and adipose tissue while similarly reducing gluconeogenesis in the liver. Thus, insulin is an additional hormonal signal that can indicate peripheral metabolic status. Insulin, a critical hormone in the regulation of glucose homeostasis, also impacts neural systems through the hypothalamus. It does so primarily via the arcuate nucleus of the hypothalamus, which has very high expression of insulin receptors. The effects of insulin on plasma glucose levels and hepatic gluconeogenesis are well known, but it has also been demonstrated that insulin activity in the CNS is important in the normal regulation of body weight. Several studies also indicate the importance of insulin signaling at the level of the hypothalamus in the integration of several peripheral metabolic signals including ghrelin, a peptide produced by the gut which is largely considered a "hunger hormone." Ghrelin activates neuropeptide-Y (NPY) neurons in the arcuate and inhibits pro-opiomelanocortin (POMC) arcuate neurons. Thus, insulin can have effects not only on its own but also by altering the effects of other hormones in the brain.

A well-known complication of insulin and glucose signaling, and in many cases related to obesity, is insulin resistance and type 2 diabetes (T2D). There are many pathways to insulin resistance and eventual T2D. One pathway involves excess insulin in the plasma which causes cells to downregulate many components of insulin signaling and glucose handling, including the decrease in levels of glucose transporter 4 (GLUT4) in cellular membranes. The decrease of GLUT4 leads to increased levels of extracellular glucose, which then causes pancreatic beta-cells to respond with increased insulin production in an attempt to regulate plasma glucose. Eventually, beta-cells become "exhausted" through several hypothesized pathways

including inflammation and eventual cell death. This then results in insufficient insulin production when glucose levels rise, such as after a meal, thus requiring additional exogenous insulin in order to restore balance. In the brain, T2D has several effects, including the reduction of GLUT4 in many brain areas important not only in metabolic function but also in cognition and mood. It is still unclear how T2D actually modifies brain circuits, but several reports demonstrate that individuals with T2D have a higher risk of developing vascular or Alzheimer's-related dementia. It is thought that alterations of cerebral glucose levels throughout life may contribute to this risk as individuals progress from the onset of T2D to living with the disease for many years. Thus, the effects on the brain may be related to the shift from unconstrained hyperglycemia early in life to the persistent hypoglycemia as T2D is established. This can then lead to dyslipidemial and hypertension and eventually to vascular damage within the brain. It is clear that defects in glucose and insulin signaling have important roles to play in the development of obesity and diabetes, and that once T2D is established, the continuing glucose and insulin dysregulation can lead to negative effects on brain and cognition.

While glucose and insulin are important indicators of short-term energy availability and can track the intake of nutrients, other neuroendocrine signals are responsible for signaling the longer-term energy status of the organism. These signals can then affect central feeding and metabolic circuits to help guide both motivated behaviors as well as potential shifts in metabolic strategies. One such factor with important hypothalamic actions is the hormone leptin, a peptide hormone secreted from adipose tissue that can act in the hypothalamus to affect feeding and metabolism. A landmark finding in metabolic research was that leptin or leptin receptor-deficient rodents become morbidly obese, and that humans carrying similar mutations show marked obesity (Friedman and Halaas 1998).

Ordinarily, leptin levels increase in proportion with adiposity and provide a negative feedback signal to neurons of the hypothalamus that regulate energy balance. This allows lean individuals to resist changes to their body weight despite access to highly palatable, high-calorie foods. In contrast, obese individuals overeat despite elevated leptin levels, suggesting that hypothalamic leptin resistance plays a central role in their susceptibility to weight gain. A prevailing model forwarded to explain this difference (i.e., the mechanism underlying obesity) involves resistance to the weight-maintaining action of the hormone leptin. However, selective leptin resistance in the periphery and the CNS adds a level of complexity to this and can occur at different levels of the leptin-signaling cascade. Thus, determining the underlying causes of leptin resistance and developing therapies to reverse it are active areas of research.

Recent work has provided a potential mechanism that contributes to the development of leptin resistance and obesity. As rats overeat during the first few days of high-fat diet (HFD), they show increased hypothalamic–pituitary–adrenal (HPA) axis tone and inflammatory responses. With sustained consumption of HFD, 25% of the critical weight-reducing (POMC) neuronal population is lost, leading to reduced responsiveness to leptin and presumably increased susceptibility to obesity (Thaler et al. 2012). As with other conditions involving brain injury such as stroke, multiple

sclerosis, and Alzheimer's disease, this neuronal damage triggers a CNS-specific wound-healing response involving neighboring astrocytes and microglia. This "reactive gliosis" is observable specifically within the hypothalamus and is likely not a brain-wide response. Remarkably, this gliosis is also seen on MRI scans taken from obese mice and humans, suggesting that this damage process may be a common mechanism underlying obesity. Thus, overconsumption of a fat-rich diet may elicit potentially permanent changes in the hypothalamus that promote obesity (Dorfman and Thaler 2015). More optimistically, these findings provide a new direction for obesity drug design, shifting away from the current emphasis on improving leptin sensitivity toward targeting the structural changes of obesity including neuronal damage and reactive gliosis. Currently, tools are being developed to modify glial cell function both to harness the neuroprotective capacity of these cells as a potential obesity treatment and to clarify the role of glia in energy homeostasis more generally.

Another mechanism linking leptin signaling within the hypothalamus and the regulation of weight and feeding is the endocannabinoid (eCB) system, which is an important regulator of feeding and metabolism in its own right (Silvestri and Di Marzo 2013). The relationship between leptin and eCB activity in the regulation of feeding seems to be inverse, with administration of leptin-reducing eCB hypothalamic content together with reductions in feeding. Along similar lines, food deprivation results in a reduction in leptin and an increase in hypothalamic eCBs. Completing this circuit, blockade of cannabinoid type 1 receptor (CB1r) signaling suppressed the rebound feeding that occurred following food deprivation. One mechanism by which leptin regulates eCB signaling is through an induction of eCB hydrolysis via the enzyme fatty acid amide hydrolase (FAAH). Leptin administration causes a rapid increase in the hydrolytic activity of hypothalamic FAAH, which caused reduction in the tissue levels of the eCB anandamide (AEA). Moreover, leptin-deficient mice have reduced FAAH-mediated AEA hydrolysis and a basal increase in AEA content in the hypothalamus. This is important since local AEA administration into the hypothalamus can induce feeding, even in presated animals. As such, there are multiple mechanisms by which leptin resistance within the hypothalamus occurs, and both inflammation and eCB signaling, as well as possible interactions between these systems, may be important in these domains.

Glucocorticoids in Obesity: Central and Peripheral Mechanisms

Cortisol (CORT) is an important metabolic and stress hormone. Plasma CORT is largely controlled by the hypothalamic–pituitary–adrenal (HPA) axis, which is engaged during the "fight-or-flight" response. There is also a well described circadian rhythm of plasma CORT present in many species, with plasma levels reaching their peak just before onset of activity. One of the roles of CORT in the context of both the stress response and normal daily rhythms is mobilization of glucose stores in many body compartments, including the liver and the skeletal muscle (Cooper et al. 2015). CORT raises plasma glucose levels by increasing the rate of hepatic gluconeogenesis while also inhibiting peripheral glucose utilization. Thus, increased

levels of CORT are usually associated with increased plasma glucose levels, an important way to increase available energy either to deal with an acute stress or to prepare for the onset of daily activity. Recent work has also provided evidence for rapid effects of CORT at the level of the brainstem, an area already discussed as being critical in the detection and regulation of circulating glucose (Ragozzino et al. 2020). Normal HPA activity is important to maintain health, in many contexts. In the context of obesity and metabolic syndrome, dysregulation of the HPA has been documented in many metabolic disorders. While stress has been linked to obesity, these links are not always clear, as numerous studies show that chronic stress results in a blunted weight gain or even weight loss. However, it is evident that disruption of CORT results in metabolic changes, perhaps the best known of which is the metabolic syndrome phenotype observed in patients suffering from hypercortisolemia due to iatrogenic or organic Cushing's syndrome. How disrupted HPA functioning contributes to the development of the risk factors associated with metabolic syndrome remains unknown. In mouse studies, high-CORT treatment results in hyperphagia, obesity, and dramatically increased plasma leptin and insulin. The very high leptin levels observed in CORT-treated mice are equivalent to those observed in diet-induced obese mice and are coupled with their hyperphagia and high body weight, suggesting that high-CORT treatment results in leptin resistance. As discussed, high levels of leptin suggest that metabolic needs are being met, or exceeded, and hence under normal conditions, feeding is suppressed. But in the case of excessively high levels of CORT, leptin signaling is impaired, and this important endocrine signal of energy availability is without effect. Mechanistically, it remains unknown whether CORT directly drives production and release of leptin from adipocytes or whether secondary effects of CORT result in the observed increase in leptin. However, significant work has been undertaken looking at both the in vivo and in vitro stimulation of leptin production by CORT. In vivo, dexamethasone stimulates plasma leptin expression and elevates adipose tissue expression of leptin. In parallel, in vitro studies demonstrate that dexamethasone increases leptin mRNA in adipose cultures quickly (e.g., within 24–48 h). Thus, there exists a complex interactive relationship between CORT and leptin that may vary depending on the tissue examined.

Interactions Between Glucocorticoids and Insulin

In comparison, and as discussed above, insulin serves as a key signal of plasma glucose levels, with high levels of insulin-signaling organs and tissues to take up glucose from the blood stream. The CORT–insulin interaction is a key issue in the context of obesity and peripheral cues that can drive individuals to an obese phenotype. This is especially true when one considers that in some instances, CORT and insulin act to resist each others' effects, while in other cases, they act in an additive or synergistic fashion. The work of Dr. Mary Dallman and colleagues has been indispensable to our understanding of the interactions between the stress axis and metabolism (Dallman 2010). Work from this group has shown that stress and

stress hormones alter food preferences, with a clear dose-dependent effect of CORT on sucrose, saccharin, and lard. Insulin is usually anorectic, with inhibitory actions on orexigenic neuropeptide-Y (NPY) neurons. This is coupled with excitatory effects on anorexigenic hypothalamic arcuate POMC. However, in a model of induced T2D (i.e., streptozotocin treatment), CORT and insulin treatment increases consumption of lard in a dose-dependent manner. This highlights an interactive role between metabolic and stress hormones and further underscores that disruptions in different hormone systems can lead to unexpected and integrative outcomes that may contribute to obesity.

Extrahypothalamic Circuits: Focus on the Reward System

While the hypothalamus is vitally important for both normal and abnormal metabolic function, other brain areas play a role in the development of obesity, as well as key targets of peripheral signals that are altered in obese individuals. As discussed above, feeding is normally regulated by the circulating peptides, insulin and leptin, that transmit satiety signals to the brain. Both insulin and leptin are altered in obesity and can have marked effects on extrahypothalamic brain regions.

Insulin accesses the brain through an active transport mechanism across the blood–brain barrier. Within the brain, insulin can signal through insulin receptors expressed in many brain regions, including the ventral tegmental area (VTA). The VTA is a critical brain region for reinforcement and reward seeking. There are multiple theories for the role of insulin in the VTA, but growing evidence supports a role for insulin in the VTA as a mechanism to suppress feeding behavior, as intra-VTA insulin injections inhibit many feeding behaviors, including a decrease in palatable food consumption after satiation. Insulin treatment of the VTA not only affects food consumption but also can decrease learned associations between the food and environmental context, such as food-anticipatory behavior and conditioned place preference to food. In this context, it may be that VTA insulin signaling suppresses processes involved in learned associations between contextual (e.g., visual and/or olfactory) stimuli and food (Labouebe et al. 2013).

Consistent with the behavioral findings that intra-VTA insulin suppresses the salience of learned food-predicting cues, insulin causes a long-lasting reduction in excitatory synaptic transmission onto dopamine neurons of the VTA. The mechanisms for these changes are not fully understood, but insulin receptor activation leads to a postsynaptic activation of several signaling molecules, including insulin receptor tyrosine kinase, AKT, and mTOR. The activation of these pathways can then lead to increased synthesis of the endocannabinoid 2-arachidonyl glycerol (2-AG). Since endocannabinoids are retrograde signaling molecules, 2-AG diffuses back to the presynaptic neuron where it activates CB1r, thus reducing further glutamate release and reducing overall excitatory transmission in the circuit. In addition to these processes, insulin can also reduce extracellular dopamine concentrations via an increase in the number and/or function of dopamine transporters, which has the overall effect of increasing reuptake of dopamine. This further reduces the activity of

these synapses. Therefore, insulin, a hormone that is crucial for normal metabolic functions and whose activity is significantly impacted in obesity, can suppress excitatory inputs to VTA dopamine neurons, thereby reducing information about food-related cues. In normal individuals, the increase in insulin following a meal can serve as a "brake" within the VTA. It is possible that in obese individuals, the inhibitory "brake" provided by VTA insulin signaling is compromised, either because the receptor has become desensitized or because peripheral production of insulin is reduced. Without this feedback, feeding may continue even though the individual is sated and metabolic demands are met. Thus, defects in insulin signaling in extrahypothalamic brain regions can also contribute to increased food consumption and amplification of the metabolic dysregulation.

Insulin is not the only metabolic hormone that can impact extrahypothalamic brain regions. Leptin also seems to play an inhibitory role in VTA dopaminergic synapses. The actions of leptin could be through two different routes: a postsynaptic route or a presynaptic route. Postsynaptically, leptin can act on dopamine neurons to reduce firing rate. In addition, leptin-deficient mice have decreased vesicular dopamine in the VTA and reductions in activity-dependent dopamine release in the nucleus accumbens, the major target of the VTA in the reward circuit. Presynaptically, leptin can act to inhibit glutamate release onto dopamine neurons. This means that in obese individuals, where high leptin levels can lead to leptin resistance, the processes by which leptin can inhibit feeding and food-related activity in the reward circuit are compromised. Thus, both leptin and insulin can act through parallel mechanisms in the VTA to inhibit aspects of ingestive behavior, and both of these peripherally derived hormones are impacted by obesity.

Circadian Influences on Obesity: A New Perspective

Exogenous drivers of obesity are an active area of research, spanning from environmental mediators to social cues. Recently, circadian (daily) rhythms, and disruption of these rhythms by light, are being actively pursued as major contributors to an individual's vulnerability to become overweight and obese. Circadian rhythms are rhythms in physiology and behavior that are both phylogenetically ancient and incredibly well conserved between species. In mammals, the master circadian clock is the suprachiasmatic nucleus (SCN) of the hypothalamus, a brain region we have previously discussed as being essential for regulation of many feeding and metabolic processes. The SCN generates circadian rhythms and is also responsible for synchronizing these rhythms to the external light–dark (LD) cycle. Complementing this central clock are "peripheral oscillators" found throughout the brain and body, which are widely conceived as being responsible for setting "local time" in various organs and tissues. Intriguingly, these peripheral clocks are synchronized by numerous inputs, including rhythms of circulating glucocorticoids, feeding, and body temperature (Hastings et al. 2003). Thus, the circadian system is well integrated with the central and peripheral systems that regulate metabolism and feeding.

At the molecular level, circadian "clock genes" play an important role in metabolic function. Work by Turek and colleagues has shown that mice carrying the CLOCK mutation, which causes the central pacemaker and peripheral oscillators to eventually become arrhythmic, become obese when compared to their wild-type littermates. To compound these basal effects of a circadian mutation on metabolism and obesity, when exposed to HFD, CLOCK mice become obese more rapidly and to a greater extent than normal chow-fed mice. A similar pattern of results can be obtained using elegant studies that can control circadian clock genes at the tissue level. Mice with a conditional CLOCK locus mutation only in the islet cells of the pancreas develop both obesity and T2D several weeks after gene deletion, clearly demonstrating that circadian clocks both at the tissue and whole organism levels contribute to maintaining normal weight and metabolic function (Marcheva et al. 2010).

While the genetic studies are remarkable, most humans do not suffer from mutations in these genes, let alone mutations only in certain organs. Yet, increases in obesity seem to be comorbid with changes in circadian and sleep patterns. This suggests that external factors that drive both circadian disruption and obesity may be at work. Even in the simplest organisms, circadian clocks likely evolved because of adaptive pressure to anticipate energy availability and predict changes in the environment driven by the rotation of the Earth on its axis. Because of this, the internal body clocks of our earliest ancestors were inextricably linked to the solar day for millions of years. However, over the past 100–150 years, with the advent of electric lighting and modern industry, modern humans have broken this once very tight connection between the daily activity and the solar day. This represents rapid environmental change when viewed in the context of the evolution of the circadian clock, and the epidemiological literature supports the hypothesis that disruption of the circadian clock negatively impacts health, especially metabolic function.

In humans, poor sleep and circadian disruption caused by long-term shift work is linked with increased incidences of diabetes and other risk factors for the development of cardiovascular disease (Ha and Park 2005). Social jet lag, a phenomenon by which individuals show chronically changing sleep patterns driven by social factors (i.e., early wake times on school/work days, but later wake times on the weekends), has been associated with a higher BMI. This indicates that circadian impacts on metabolic function are not restricted only to shift workers or individuals with repeatedly altered sleep–wake schedules. Patterns of human settlement on the Earth provide an additional type of epidemiological link between the environment, circadian/sleep disruption, and metabolism. For instance, living in polar latitudes presents a specific set of challenges for life, with extremely cold temperatures and profound changes in the photic environment based upon season (nearly constant darkness during "winter" and nearly constant daylight during "summer"). For humans, living at polar latitudes can significantly impact mental and physical health, including effects on mood, timing of sleep, and metabolic function. Focusing on changes in temporary visitors to the Arctic or Antarctic, several physiological and behavioral effects have been observed, including changes in energy dynamics and aerobic fitness, CORT, and plasma electrolytes. One longitudinal study found significant increases in body weight and body fat during the Antarctic winter that

seemed to occur without marked changes in food intake or activity. A separate set of studies showed clear changes in oral glucose tolerance in March versus December in the Antarctic. Given that sleep in Antarctic visitors is disrupted but can be improved by timed exposure to light suggests that at least some of the metabolic effects are mediated by circadian processes. Comparing how metabolic processes change in Arctic and Antarctic visitors to resident Indigenous populations could reveal adaptive responses over the long term or inherited genetic differences that could further enlighten the various mechanisms involved in the interplay of circadian rhythms and metabolism.

As noted, the specific mechanisms for these apparent environmentally driven effects remain unclear, but clinical studies in human populations demonstrate a strong relationship between misaligned sleep and glucose homeostasis, showing that even short-term misaligned sleep and circadian clocks can lead to diabetes-like plasma glucose levels. Basic research has started to explore these phenomena and has begun to investigate the links between changes in circadian light–dark cycles and physiological and psychological disorders. Thus, exploring how environmental factors affect development and trajectory of obesity and metabolic dysregulation can provide a powerful compliment to molecular and genetic studies. Recent work has explored how disrupting the normal light–dark environment of mice affects metabolic function. For instance, exposing mice to dim light at night results in significant increases in body weight *without* overall increases in food consumption. Instead, mice start to consume more food during the daytime (when they should be asleep). A series of studies has demonstrated that housing WT C57BL6 mice in a shorter 20 h cycle (10 h light: 10 h dark) leads to excessive weight gain, metabolic dysregulation as measured by leptin and insulin levels, and an altered relationship between plasma insulin and glucose, suggesting a prediabetic or diabetic state (Karatsoreos et al. 2011). These findings are also associated with a blunting of the rhythms of "clock gene" expression (e.g., *Period1, Period2, Cryptochrome1, and Cryptochrome2*) in the liver and white adipose tissue. Interestingly, and perhaps fitting given its role as both a circadian synchronizer and metabolic hormone, chronic housing in 20 h days also results in a reduction of the rhythm of plasma CORT. Additional findings have shown similar patterns of effects by exposing animals to light at night, in some ways modeling the types of exposures modern humans may be subject to (Fonken and Nelson 2014). These findings in both humans and nonhuman animals show disruption of central and peripheral clock function which contributes to the development of a metabolic syndrome phenotype. However, more work is necessary to explore the mechanisms by which these altered cycles affect the peripheral and central controls of feeding and metabolic function.

Summary and Clinical Implications

This chapter demonstrates that many peripheral signals are involved in the neural control of feeding and metabolic function, which, when dysregulated, contribute to the development of obesity and metabolic syndrome. Further, the obese

pathophysiological state itself further promotes dysregulation of central neural circuits orchestrating feeding and metabolic pathways. As a result of these interactions, a capitulating feed-forward cycle takes hold, and with each cycle, the negative symptoms and effects are amplified. One potential way out of this cycle is to treat at least one of the fundamental causes, which should alter the overall trajectory of disease progression and hopefully result in arresting the disease or even potential reversal. However, the clinical treatment of obesity is extremely difficult, and as of yet, there are no comprehensive interventions that can end obesity. Nonetheless, several clinical strategies have been developed that should increase the odds of successfully reducing both weight and metabolic dysregulation. Perhaps the most common and controversial is the use of bariatric surgery.

The prevalence of surgical intervention has become increasingly more common as a main tool for treating obesity. A group of procedures collectively known as bariatric surgeries are now more common than ever. These generally include three types:

1. Roux en Y gastric bypass – gastric resection and anastomosis
2. Sleeve gastrectomy – resection of stomach to decrease gastric volume but maintain ability for secretions
3. Gastric banding – ability to temporarily decrease gastric volume with no surgical resection

Common to all three approaches is the reduction in size of the stomach, which necessarily decreases the volume of food consumed in a given meal. The first two procedures also surgically remove part of the stomach. In the case of the Roux en Y procedure it completely bypasses the duodenum. Although there is large patient-to-patient variability, some persons experience profound metabolic improvement (resolution of the metabolic syndrome diagnosis including T2D) following surgery but prior to significant weight loss, consistent with the high importance of these areas and their neural innervation for the maintenance of metabolic control and development of metabolic syndrome. While these procedures are potentially lifesaving for many people, they are not without major side effects including high surgical mortality, development of dumping syndrome, malabsorption of nutrients, and others. As such, the procedures are not without trade-offs.

Perhaps one of the most effective treatments for obesity is to prevent the cycle from taking hold in the first place. This is easier said than done for many reasons. The first law of thermodynamics, distilled and translated into metabolic terms, tells us that weight gain will occur if there is an imbalance between calories consumed and calories burned. However, this useful rule of thumb does not really elaborate on how calories can be used nor the processes by which we can modulate calorie consumption. In the human body, calories are consumed not only through explicit exercise but also through the countless biochemical processes that occur in the body, as is clearly denoted by the excess body heat generated by endotherms. Therefore, processes that alter these energy production pathways could alter the ability of an organism to efficiently burn calories. On the other hand, it is clear that many humans

do not eat just to simply restore the calories that were consumed by exercise or heat production. We eat for many different reasons apart from necessity, from coping with stress (i.e., comfort feeding) to social pressures (e.g., large holiday gatherings), and for its rewarding effects. The types of food consumed can also be modulated by these pressures, as well as economics, in that cheap, calorie-dense, food is available in large quantities and tends to be palatable. These different types of feeding are both driven by, and can also alter, brain centers not normally considered to be essential for feeding (e.g., the VTA, discussed above). Thus, while it would be ideal to suggest obesity can be cured by simply eating less and exercising more, it is no small task when the various external and internal processes at play are considered. The solution likely lies in better understanding of the complex processes underlying feeding and energy expenditure. If we gain a better understanding of the myriad molecular, cellular, hormonal, and behavioral changes that lead to an obesogenic phenotype, and how peripheral signals in obese individuals further conspire to resist changing behavior and physiology, then these interventions may not seem so daunting.

References

Andresen MC et al (2004) Differentiation of autonomic reflex control begins with cellular mechanisms at the first synapse within the nucleus tractus solitarius. Braz J Med Biol Res 37(4): 549–558

Berthoud H-R, Zheng H (2012) Modulation of taste responsiveness and food preference by obesity and weight loss. Physiol Behav 107(4):527–532

Cooper MS, Seibel MJ, Zhou H (2015) Glucocorticoids, bone and energy metabolism. Bone 82: 64–68

Dallman MF (2010) Stress-induced obesity and the emotional nervous system. Trends Endocrinol Metab 21(3):159–165

Dorfman MD, Thaler JP (2015) Hypothalamic inflammation and gliosis in obesity. Curr Opin Endocrinol Diabetes Obes 22(5):325–330

Fonken LK, Nelson RJ (2014) The effects of light at night on circadian clocks and metabolism. Endocr Rev 35(4):648–670

Friedman JM, Halaas JL (1998) Leptin and the regulation of body weight in mammals. Nature 395(6704):763–770

Gao Q, Horvath TL (2007) Neurobiology of feeding and energy expenditure. Annu Rev Neurosci 30(1):367–398

Giduck SA, Threatte RM, Kare MR (1987) Cephalic reflexes: their role in digestion and possible roles in absorption and metabolism. J Nutr 117(7):1191–1196

Grill HJ, Hayes MR (2012) Hindbrain neurons as an essential hub in the neuroanatomically distributed control of energy balance. Cell Metab 16(3):296–309

Ha M, Park J (2005) Shiftwork and metabolic risk factors of cardiovascular disease. J Occup Health 47(2):89–95

Hastings MH, Reddy AB, Maywood ES (2003) A clockwork web: circadian timing in brain and periphery, in health and disease. Nat Rev Neurosci 4(8):649–661

Karatsoreos IN, Bhagat S, Bloss EB, Morrison JH, McEwen BS (2011) Disruption of circadian clocks has ramifications for metabolism, brain, and behavior. Proc Natl Acad Sci U S A 108(4): 1657–1662

Labouebe G et al (2013) Insulin induces long-term depression of ventral tegmental area dopamine neurons via endocannabinoids. Nat Publ Group 16(3):300–308

Marcheva B et al (2010) Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. Nature 466(7306):627–631

Ragozzino FJ, Arnold RA, Kowalski CW, Savenkova MI, Karatsoreos IN, Peters JH (2020) Corticosterone inhibits vagal afferent glutamate release in the nucleus of the solitary tract via retrograde endocannabinoid signaling. Am J Physiol Cell Physiol 319(6):C1097–C1106

Ritter RC (2004) Gastrointestinal mechanisms of satiation for food. Physiol Behav 81(2):249–273

Ritter S, Li AJ, Wang Q (2019) Hindbrain glucoregulatory mechanisms: critical role of catecholamine neurons in the ventrolateral medulla. Physiol Behav 208:112568

Sartor DM (2013) Sympathoinhibitory signals from the gut and obesity-related hypertension. Clin Auton Res 23(1):33–39

Silvestri C, Di Marzo V (2013) The endocannabinoid system in energy homeostasis and the etiopathology of metabolic disorders. Cell Metab 17(4):475–490

Thaler JP, Yi CX, Schur EA, Guyenet SJ, Hwang BH, Dietrich MO, Zhao X, Sarruf DA, Izgur V, Maravilla KR, Nguyen HT, Fischer JD, Matsen ME, Wisse BE, Morton GJ, Horvath TL, Baskin DG, Tschöp MH, Schwartz MW (2012) Obesity is associated with hypothalamic injury in rodents and humans. J Clin Invest 122(1):153–162

Turicchi J, O'Driscoll R, Horgan G, Duarte C, Palmeira AL, Larsen SC, Heitmann BL, Stubbs J (2020) Weekly, seasonal and holiday body weight fluctuation patterns among individuals engaged in a European multi-centre behavioural weight loss maintenance intervention. PLoS One 15(4):e0232152