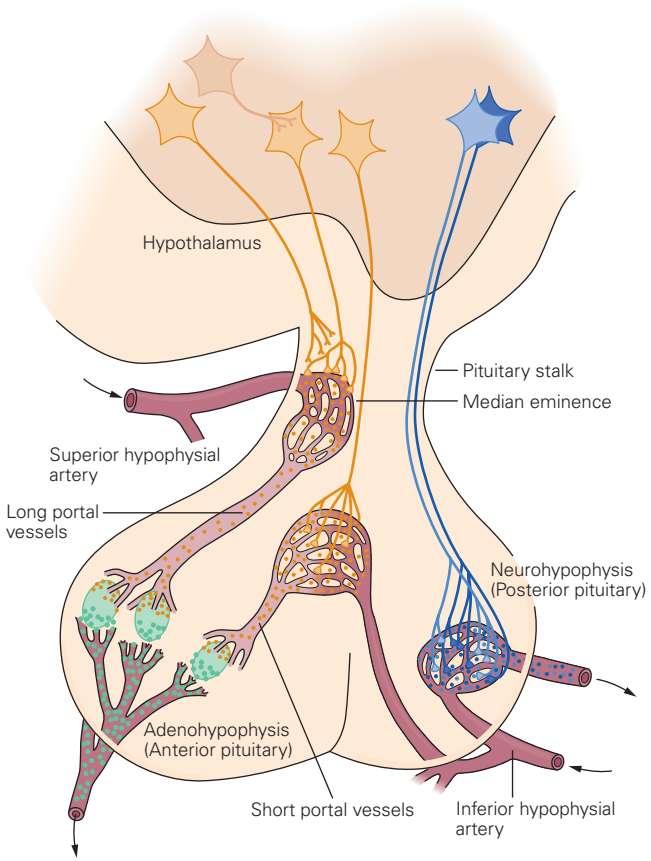



**Figure 41–12** The hypothalamus controls the pituitary gland both directly and indirectly through neuroendocrine neurons. Neurons in the magnocellular neuroendocrine system (**blue**) send their axons directly to the posterior pituitary (neurohypophysis) where they release the peptides vasopressin and oxytocin into the general circulation. Neurons in the parvocellular neuroendocrine system (**yellow**) send their axons to the hypophysial portal system in the median eminence and pituitary stalk. Portal veins transport hypothalamic hormones (peptides and dopamine) to the anterior pituitary (adenohypophysis) where they increase the release of hormones from five classic types of endocrine cells (Figure 41–11). The output of neuroendocrine neurons is regulated in large part by inputs from other regions of the brain. (Adapted from Reichlin 1978, and Gay 1972.)

### Endocrine Cells in the Anterior Pituitary Secrete Hormones in Response to Specific Factors Released by Hypothalamic Neurons

In the 1950s, Geoffrey Harris proposed that the anterior pituitary, or *adenohypophysis*, is regulated indirectly by the hypothalamus. He showed that the hypophysial portal veins, which carry blood from the hypothalamic median eminence to the anterior pituitary, transport factors released from hypothalamic neurons that control anterior pituitary hormone secretion (Figure 41–12). In the 1970s, Andrew Schally, Roger Guillemin, and Wylie Vale determined the structure of a group of hypothalamic peptide hormones that control pituitary hormone secretion from the five classic endocrine cell types in the anterior pituitary. These hormones, which are released into the median eminence by hypothalamic neurons, fall into two classes: releasing hormones and release-inhibiting hormones. Only one anterior pituitary hormone, prolactin, is under predominantly inhibitory control (mediated by dopamine).

The *parvocellular neuroendocrine motor zone* of the hypothalamus is centered along the wall of the third ventricle (Figure 41–2A) and contains neurons that project to and release their hormones into the median eminence. The parvocellular neurons releasing *gonadotropin-releasing hormone* (GnRH) are atypical in that they are scattered in a continuum extending from the medial septum through to the mediobasal hypothalamus. They are controlled by upstream neurons that release *kisspeptin*. The remaining parvocellular neuroendocrine neurons lie within the paraventricular and arcuate nuclei and the short periventricular region between them (Figures 41–2 and 41–11).

Distinct pools of neurons in and around the paraventricular nucleus release *corticotropin-releasing hormone* (CRH), *thyrotropin-releasing hormone* (TRH), or *somatostatin* (or growth hormone release-inhibiting hormone) (Figure 41–11). The CRH neurons control the release of anterior pituitary adrenocorticotropic hormone (ACTH), which in turn controls the release of cortisol (glucocorticoids) from the adrenal cortex. Thus, this pool of CRH neurons is the "final common pathway" for all centrally mediated glucocorticoid stress hormonal responses. The arcuate nucleus contains two pools of parvocellular neuroendocrine neurons. One group releases *growth hormone–releasing hormone* (GHRH) and the other dopamine, which inhibits prolactin secretion. Some of the dopaminergic neurons are distributed dorsally as far as the paraventricular nucleus.

The axons of all these parvocellular neuroendocrine neurons travel in the hypothalamo-hypophysial tract and end in the specialized proximal end of the pituitary stalk, the median eminence (Figure 41–12). There, in a region of capillary loops in the external zone of the median eminence, the axon terminals release the various hypophysiotropic factors. While the median eminence is within the brain, it is considered outside the blood–brain barrier. This is due to the fenestrated nature of the median eminence

**Table 41–3** Hypothalamic Substances That Release or Inhibit the Release of Anterior Pituitary Hormones

| Hypothalamic substance | Anterior pituitary hormone |
|---|---|
| *Releasing:* | |
| Thyrotropin-releasing hormone (TRH) | Thyrotropin (TSH), prolactin (PRL) |
| Corticotropin-releasing hormone (CRH) | Adrenocorticotropin (ACTH), β-lipotropin |
| Gonadotropin-releasing hormone (GnRH) | Luteinizing hormone (LH), follicle-stimulating hormone (FSH) |
| Growth hormone–releasing hormone (GHRH or GRH) | Growth hormone (GH) |
| *Inhibiting:* | |
| Prolactin release-inhibiting hormone (PIH), dopamine | Prolactin |
| Growth hormone release-inhibiting hormone (GIH or GHRIH; somatostatin) | Growth hormone, thyrotropin |

capillaries, which allow diffusion of the hypophysiotropic factors into the portal circulation. The median eminence capillary loops are the proximal end of the hypophysial portal system of veins that carry the factors to the anterior pituitary, where they act on cognate receptors on the five types of endocrine cells (Figure 41–12 and Table 41–3).

## Dedicated Hypothalamic Systems Control Specific Homeostatic Parameters

### Body Temperature Is Controlled by Neurons in the Median Preoptic Nucleus

*Body Temperature Reflects the Balance Between Heat Production and Loss*

The body generates heat through all of its exothermic biochemical reactions and ion fluxes. These processes can be greatly increased above a baseline level, the resting metabolic rate, by exercise and shivering (both of which increase skeletal muscle heat production), by the digestion and assimilation of food (the so-called thermic effect of food), and by sympathetic stimulation of thermogenic activity in brown adipose tissue (Box 41–1).

The body loses heat by radiation, convection, conduction (if immersed in cool water), and endothermic evaporation of either sweat from the skin or moisture from the respiratory tract (a process augmented in some species by panting). The defensive reaction to cold, in addition to producing heat, involves sympathetically mediated cutaneous vasoconstriction and piloerection (goose bumps). By sending less blood to the skin, vasoconstriction conserves core temperature. Piloerection helps insulate the skin by creating a layer of motionless air near the skin's surface. Conversely, defenses against overheating include inhibition of sympathetic pathways that activate cutaneous vasodilation and brown adipose tissue. Voluntary behavioral responses like taking a swim or putting on a sweater play a particularly important role in thermoregulation.

### Box 41–1 Brown Adipose Tissue, Bioenergetics, and Sympathetically Driven Thermogenesis

Brown adipose tissue is a remarkably specialized heat-producing tissue that is especially abundant in newborns and small mammals, but is also found in adult humans. It has a rich blood supply for delivery of fuel and oxygen and for removal of heat and is densely innervated by postganglionic sympathetic nerves. Brown adipocytes, the producers of heat, are found in concentrated deposits in and around the core and also as isolated cells within larger white adipose tissue depots.

Sympathetic stimulation of β-adrenergic receptors activates uncoupling protein-1 (UCP1), a mitochondrial proton transport protein that is unique to brown adipocytes. When activated, UCP1 "leaks" protons across the mitochondrial inner membrane into the mitochondrial matrix, down the proton electrochemical gradient. This uncouples mitochondrial respiration from adenosine triphosphate (ADP) availability, greatly increasing fuel oxidation and, importantly, the production of heat.

Exercise and shivering, on the other hand, increase heat production by using adenosine triphosphate (ATP) to perform work. The resulting increase in ADP activates proton transport into mitochondria via ATP synthase, which then increases coupled mitochondrial respiration, fuel oxidation, and ultimately the production of heat.

They usually begin before the onset of physiologic responses. Like thirst/drinking and hunger/eating, activities generated in response to cold or hot challenges are motivated behaviors.

### *Body Temperature Is Detected at Multiple Sites*

Core temperature is held relatively constant. At the shell, on the other hand, temperature fluctuates extensively because the shell is adjacent to the external environment, it has a high surface-to-mass ratio (in the case of limbs favoring heat loss over heat production), and thermal challenges dramatically affect its supply of warm blood (decreased when heat needs to be conserved; increased when heat needs to be lost).

Most primary afferents that detect temperature have their cell bodies in the spinal dorsal root ganglia. Neurons that detect noxious temperatures are part of the pain pathway (Chapter 20). Their function is to limit local tissue damage by promoting withdrawal as opposed to regulating body temperature. Neurons that respond to innocuous temperatures are often called thermoreceptors. Some thermoreceptor neurons have their endings in the skin, just below the epidermis, and these respond to shell temperature. They are predominantly, but not entirely, cold-responsive. Other thermoreceptor neurons have their endings in and around the large organs and respond to core temperature. They are also largely, but not entirely, cold-responsive. The fibers for the deep-tissue thermoreceptor neurons travel in the splanchnic nerves and, like the thermoreceptor neurons in the shell, have their cell bodies in the dorsal root ganglia. In addition, some also travel in the vagal afferent nerve. Finally, there are warm-sensing neurons in the hypothalamic medial preoptic area.

The molecular sensors utilized by thermoreceptor neurons for detecting changes in temperature are a subset of excitatory transient receptor potential (TRP) channels. Different TRP channels respond to different ranges of temperatures (Chapter 20). Recent studies have implicated specific TRP channel types in various forms of sensing innocuous temperature in the three sites mentioned above: TRMP8 channels mediate cold-sensing by shell thermoreceptor neurons, and TRPM2 channels mediate warm-sensing both by somatosensory thermoreceptor neurons and by neurons in the hypothalamic preoptic area.

### *Multiple Thermoreceptor/Thermoeffector Loops Control Temperature*

Involuntary thermal regulation is controlled by a multisensor, multieffector thermoregulatory system. Thermal information from the shell and the viscera ascends via primary afferents whose cell bodies are in the dorsal root ganglia. They project to second-order neurons in the dorsal horn of the spinal cord. These neurons project via the spinothalamic tract to the lateral parabrachial nucleus where neurons relay cold-sensing and warm-sensing information to neurons in the hypothalamic MnPO. Activation of the cold-sensing or warm-sensing afferent pathways induces appropriate physiological responses aimed at increasing or decreasing body temperature.

The neurons in the MnPO that indirectly respond to cold and warmth send efferent signals via relays through the medial preoptic area, dorsomedial hypothalamus, and raphe pallidus in the ventral medulla, and from there on to the sympathetic preganglionic neurons in the intermediolateral nucleus of the spinal cord. These latter neurons excite postganglionic sympathetic neurons that project to blood vessels, sweat glands, and arrector muscles of hair follicles to control cutaneous blood flow, sweating, and piloerection, respectively, as well as to brown adipose tissue to control thermogenesis. In addition, cold causes shivering when gamma motor neurons in the ventral horn of the spinal cord are activated by excitatory neurons in the raphe pallidus (Chapter 32). The resultant contraction of intrafusal muscle fibers within muscle spindles activates IA afferents from the spindles to alpha motor neurons. This proprioceptive feedback increases activity of alpha motor neurons, as well as their propensity to undergo rhythmic bursts of activity, causing increased muscle tone and frank shivering.

The neural pathways controlling voluntary thermoregulatory behaviors involve the same thermoreceptor pathways. Stimulation of warm-sensitive neurons in and around the MnPO evokes dramatic cold-seeking behavior, decreases heat production, and increases heat loss. The conscious perception of body temperature relies upon the same first-order thermoreceptor neurons, but the afferent pathway diverges to activate second-order neurons in the dorsal horn, which project directly or indirectly to neurons in the ventromedial nucleus of the thalamus. These thalamic neurons project to the insular cortex.

From the above discussion, it is clear that there is neither a set point for body temperature nor a "thermostat" that maintains it at 37°C. Instead, as mentioned earlier, an apparent set point for body temperature emerges as a settling point controlled by multiple sensorymotor feedback loops containing thermoreceptors and thermoeffectors. It is a major achievement of evolution that this multicomponent afferent/efferent system is

so effective in keeping the temperature of the body core remarkably constant.

*Dysregulation of Circuits Controlling Temperature Causes Fever*

In the past, when the set point view of thermoregulation was dominant, fever was thought to be caused by raising the body temperature set point—a view that still persists in major medical textbooks. Based on the advances described above, fever is now thought to arise through modulation of the afferent/efferent loops, particularly as they traverse the hypothalamic preoptic area. Prostaglandin E2, generated by the action of inflammatory cytokines on endothelial cells in the preoptic area, inhibits warm-activated GABAergic neurons in the MnPO, thus disinhibiting the effector pathways that promote cutaneous vasoconstriction, brown adipose tissue thermogenesis, and shivering. Nonsteroidal anti-inflammatory drugs, such as aspirin, ibuprofen, and acetaminophen, reduce fever by inhibiting hypothalamic generation of prostaglandin E2.

## Water Balance and the Related Thirst Drive Are Controlled by Neurons in the Vascular Organ of the Lamina Terminalis, Median Preoptic Nucleus, and Subfornical Organ

*Changes in Blood Osmolarity Cause Cells to Shrink or Swell*

Driven by osmosis, water moves freely across cell membranes. This has a number of important consequences. First, because of its large size, the intracellular compartment contains two-thirds of the body's water. Second, if blood osmolarity changes from its normal value (~290 mOsm/kg)—because water is gained by drinking or lost by renal excretion and by sweating, or because solutes have been added by eating (or by drinking, eg, sea water—1000 mOsm/kg)—water will move and the osmolarity of all compartments will equilibrate, including the intracellular one.

Because the intracellular content of osmotically active molecules is relatively fixed over the short term, increases in blood osmolarity cause cells to shrink, and conversely, decreases cause cells to swell. This is particularly dangerous for the brain because it is encased by the rigid skull. With extreme hyperosmolarity (too little water), the brain shrinks, pulling away from the skull and tearing blood vessels. With hypo-osmolarity (too much water), the brain swells, causing cerebral edema, seizures, and coma. To prevent such incidents, the brain acts to maintain normal osmolarity. It does this by detecting changes in osmolarity and then regulating the motivation to drink (thirst) and the kidney's capacity to excrete water.

*Osmolarity Is Affected When Water Is Lost or Gained and When Food Is Ingested*

Water is gained by drinking and, to a small degree, by the oxidation of fuel (fuel + $O_2 \rightarrow CO_2 + H_2O$). It is lost in a number of ways—by breathing (dry air in, humidified air out), via the gastrointestinal tract (especially when diarrhea is present), by sweating, and by urination. Eating also increases blood osmolarity by moving water from the blood to the gut to aid digestion and by adding solutes to the bloodstream as food is broken down and absorbed.

Because of these effects, there are significant interactions between neural systems that control hunger and thirst. For example, eating is such a significant osmotic challenge that dehydration and its associated hyperosmolarity strongly suppress hunger (dehydration-induced anorexia). Conversely, the act of eating itself, even in an individual with normal water content, rapidly stimulates thirst so as to mitigate the anticipated, eating-induced increase in osmolarity.

*Vasopressin Released From the Posterior Pituitary Regulates Renal Water Excretion*

The ability of the kidney to excrete water is tightly controlled by vasopressin. When it is absent, humans can excrete up to approximately 900 mL/h of urine, and when it is at maximal levels, humans excrete as little as approximately 15 mL/h. Vasopressin decreases water excretion by increasing its reabsorption from urine by the kidney.

*Osmolarity Is Detected by Osmoreceptor Neurons*

The brain maintains water balance by monitoring sensory input from osmoreceptors—sensory neurons that respond to osmolarity—which reflects the body's state of hydration. Osmoreceptor neurons are found in the periphery and on neurons in and around the hypothalamus. The central osmoreceptors monitor systemic osmolarity, while the peripheral osmoreceptors monitor osmolarity in and around the gut and related structures.

*Peripheral Osmoreceptors Allow Changes in Systemic Osmolarity to Be Anticipated*

Sensory information about peripheral osmolarity enables the brain to make preemptive changes in thirst

and vasopressin secretion that anticipate and mitigate future shifts in systemic osmolarity, such as the decrease that occurs with drinking or the increase that occurs with eating. Such regulation serves to prevent overshooting normal osmolarity, which would otherwise occur when previously ingested water, which has not yet affected systemic osmolarity, is slowly absorbed from the gut. Indeed, when a dehydrated, hyperosmolar individual ingests water, thirst and vasopressin secretion rapidly decrease, well before systemic osmolarity falls. The identity of peripheral osmoreceptors is unknown.

### *Central Osmoreceptors and the Afferent/Efferent Circuits Control Water Balance*

Three nuclei in the lamina terminalis, which forms the anterior wall of the third ventricle, play a key role in detecting and in responding to disturbances in systemic osmolarity (Figure 41–13). From ventral to dorsal, they are the OVLT, the MnPO, and the SFO. The OVLT and SFO are circumventricular organs, and like the previously discussed median eminence, they lie outside the blood–brain barrier. Because of this, neurons in these two nuclei can rapidly detect changes in blood osmolarity as well as blood-borne circulating factors that are unable to cross the blood–brain barrier (an important example being angiotensin II).

Consistent with this arrangement, osmoreceptor neurons in the OVLT and SFO make extensive connections to neurons in the MnPO. While MnPO neurons themselves do not directly sense osmolarity, they are indirectly responsive to osmolarity via relays from the OVLT and SFO. While all neurons in the OVLT and SFO appear to be dedicated to the regulation of water balance, some neurons in the MnPO are involved in regulation of body temperature (as noted earlier), cardiovascular function, and sleep. Regulation of water balance or body temperature is carried out by subsets of modality-specific neurons in the MnPO.

Neurons from all three lamina terminalis nuclei send dense excitatory projections to secretory vasopressin neurons in the paraventricular hypothalamic nucleus (PVH) and supraoptic nucleus. As described below, these three lamina terminalis nuclei are also able to cause thirst.

Central osmoreceptors, and probably also peripheral osmoreceptors, detect changes in osmolarity by

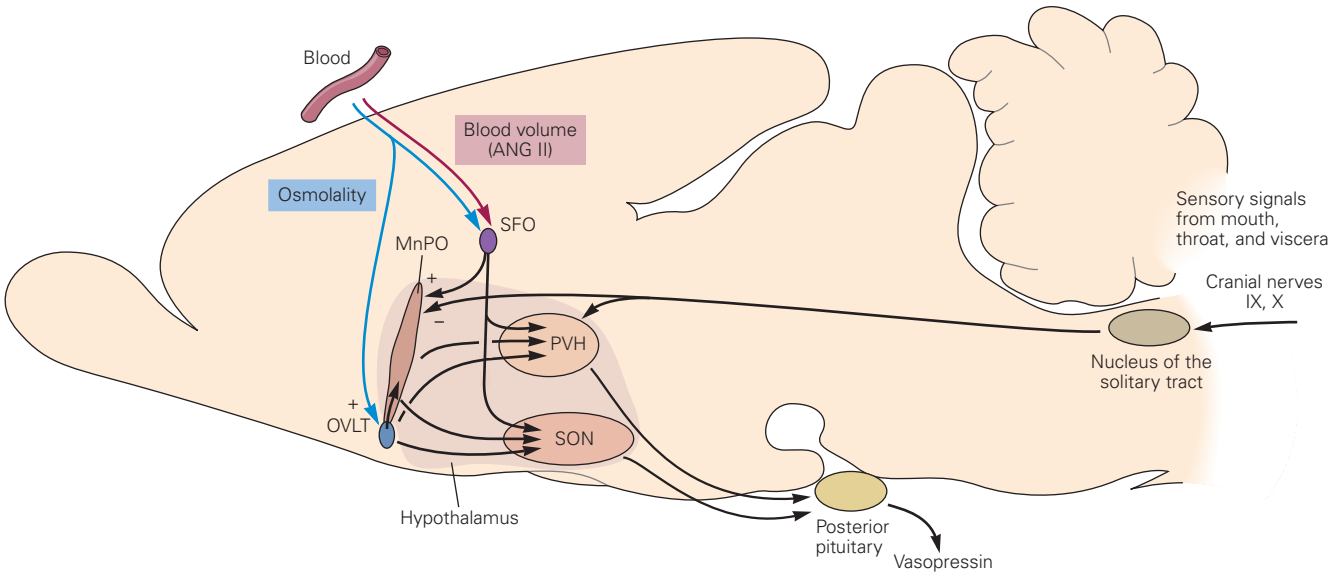



**Figure 41–13** **Neural and endocrine components combine to regulate fluid balance.** The circuitry is shown in a sagittal section through the rat brain. Information from baroreceptors in the circulatory system and from sensory receptors in the mouth, throat, and viscera is conveyed to the nucleus of the solitary tract and neighboring structures in the caudal brain stem through the glossopharyngeal (**IX**) and vagal (**X**) nerves. The hormone angiotensin II (**ANG II**) provides the brain with an additional signal concerning low blood volume. Circulating angiotensin II is sensed by receptors in the subfornical organ (**SFO**); SFO neurons project to the median preoptic area (**MnPO**), paraventricular nucleus of the hypothalamus (**PVH**), supraoptic nucleus (**SON**), and the vascular organ of the lamina terminalis (**OVLT**). The osmolality of the blood is sensed by receptors in and near the OVLT that project to the MnPO, PVH, and SON. Neurosecretory cells in the PVH and SON nuclei trigger release of vasopressin from the posterior pituitary, thus decreasing water excretion by the kidney. (Adapted, with permission, from Swanson 2000.)

responding to changes in cell volume. Shrinking or swelling, which increases or decreases, respectively, their cation permeability, causes increases or decreases in firing rate.

Decreased intravascular volume—for example, that due to acute blood loss—also potently stimulates thirst and vasopressin secretion. Low blood volume is detected by the kidney, which increases its secretion of renin. Renin is a protease that converts circulating angiotensinogen to *angiotensin I* (ANG I). ANG I is then further cleaved by angiotensin-converting enzyme in the lung, generating *angiotensin II* (ANG II). ANG II excites SFO neurons that directly, and also via a relay in the MnPO, drive vasopressin neurons and presumptive thirst neurons.

### *Thirst Is Controlled by Neurons in the OVLT, MnPO, and SFO*

As with vasopressin secretion, all three lamina terminalis structures participate in generating the motivational state of thirst, the desire to seek and ingest water. Lesion of all three structures completely blocks dehydration- and ANG II–induced thirst, as well as secretion of vasopressin. Electrical stimulation of these structures, on the other hand, elicits drinking. Activation of excitatory glutamatergic neurons in the SFO and MnPO induces intense drinking in an otherwise water-satiated mouse within seconds.

Thus, excitatory neurons in the SFO and MnPO, and likely also in the OVLT, have a remarkable capacity to induce thirst. Importantly, the behavior induced is specific—only water drinking occurs. Notably, the excitatory SFO neurons driving this behavior are the same subset of SFO neurons that are activated by dehydration and that express ANG II receptors. The downstream pathway by which these neurons stimulate thirst is presently unknown.

The activity of both the thirst neurons in the SFO and vasopressin neurons in the SON and PVH decreases or increases rapidly in response to sensory cues, such as drinking or eating, respectively, that anticipate future homeostatic disturbances. This rapid regulation occurs independent of any changes in systemic osmolarity and is therefore independent of feedback; hence, it is an example of feedforward control. The likely function of this feedforward regulation is to anticipate disturbances, institute preemptive corrective actions, and thus greatly reduce or eliminate their impact.

In summary, years of research have led to a clear model. Dehydration (water deficiency) increases the activity of neurons in the SFO and OVLT, and in the MnPO via relays from the SFO and OVLT, and this increase in activity enhances thirst and vasopressin secretion. As we shall see, a similar general system, but with different neural structures, controls caloric deficiency–based regulation of hunger and energy metabolism.

## Energy Balance and the Related Hunger Drive Are Controlled by Neurons in the Arcuate Nucleus

As with temperature and water balance, energy balance is regulated by feedback signals from the body that modulate activity of key hypothalamic neurons, which then initiate adaptive changes in both physiology and behavior. Regulation of energy balance differs, however, in important ways.

First, the feedback signals monitored are numerous and, in many cases, only very indirectly related to the key parameter, energy balance. Examples of this feedback include neural and hormonal signals from the gut, leptin from adipocytes, insulin from pancreatic beta cells, and metabolite levels in the blood. This is in striking contrast to the single, directly sensed signals monitored for thermoregulation and water balance. Second, energy can be stored as fat. The amount of energy that can be accumulated is remarkably high, so high that the energy needs of a starving person can be met for more than a month. Heat and water, in contrast, are not stored. Thus, organisms have an "energy buffer" that allows survival during prolonged deficiency.

Third, since storage has benefits, regulation of energy balance, as opposed to temperature and water balance, is asymmetric in that low energy stores are defended against very aggressively, while high stores are defended against only very weakly—hence the high prevalence of obesity in societies with calorically dense, palatable food. Fourth, energy storage can be a liability—when excessive, it promotes diseases such as obesity, diabetes, heart disease, and cancer. Finally, in circuits regulating energy balance, neuropeptides play a remarkably important role.

### *Fat Is Stored When Intake of Energy Exceeds Expenditure*

Consistent with the first law of thermodynamics, the calories that are stored as fat equal the number of calories ingested minus calories expended. While there is only one way to gain energy—by eating—there are many ways to expend energy.

Most energy is expended by biochemical reactions that are required for basic life functions. As these processes are constantly in operation, such "obligatory energy expenditure" is fixed and not regulated. Two other types of energy expenditure, however,

are dramatically different; one is voluntary physical activity, while the other is involuntary, resulting from sympathetic stimulation of brown adipose tissue and shivering. Sympathetically controlled energy expenditure, often referred to as adaptive thermogenesis, is controlled by the brain. Its function is to respond to perturbations in temperature and in energy stores.

### *The Intake and Expenditure of Energy Are Usually Matched*

For most individuals, body fat stores are relatively constant over time. Thus, calories ingested roughly equal calories expended. A simple calculation demonstrates this point. An average middle-aged person expends 3,392 kcal per day (kcal corresponds to the common term "calorie"). Over the course of a year, this typical person gains 350 g of fat (which equates to 9 kcal of fat per day). Thus, on average, 9 kcal extra must have been consumed per day to account for this gain. This is the amount of energy found in 4% of a typical candy bar or expended by walking about 150 meters. Thus, the mismatch between intake and expenditure (9 kcal) is tiny—only 0.27% of total energy expenditure.

Such close matching is the result of powerful homeostatic mechanisms that use feedback from the body to regulate intake and expenditure. As is true for regulation of temperature and osmolarity, the constancy of body weight, and the close matching between intake and expenditure, is unrelated to any specific "set point." Instead, this remarkable control is the emergent settling point of multiple afferent/efferent feedback loops.

### *Obesity Is Caused by Genes and Recent Lifestyle Changes*

Dysregulation of the above-mentioned afferent/efferent feedback loops results in obesity. While some cases of obesity are due to known mutations in genes required for homeostatic regulation, most are of undetermined cause. Of these, many are likely due to multiple mutations, many of which are uncharacterized. Because the incidence of obesity in Western societies has increased greatly in recent years, too fast to be due to new mutations, changes in diet and physical activity must also play an important role. Homeostatic systems that evolved to achieve energy balance in hunter-gatherers are likely overwhelmed by abundant, palatable, calorically dense food.

But even in our modern obesogenic environment, there are still large variations in fat stores: Only 41% to 70% of interindividual variation in fat stores can be attributed to genetic factors. Thus, genetic predisposition and environment together cause obesity. Of interest, many of the predisposing genetic loci identified to date involve genes that affect brain function.

### *Multiple Afferent Signals Control Appetite*

The major afferent signals affecting energy balance can be divided into two major categories. (1) Short-term signals from cells that line the gastrointestinal tract report the status of food in the gut. All but one of these signals increase with eating and function to terminate meals; the exception is ghrelin, which increases with fasting and stimulates hunger. (2) Longer-term signals report the status of energy reserves (ie, fat stores). These include the pancreatic hormone insulin and the adipocyte hormone leptin, both of which are released in proportion to fat stores. Their levels, especially that of leptin, inform the brain whether fat stores are adequate (Figure 41–14A).

*Signals From the Gut Trigger Meal Termination.* During eating, as food enters the stomach and intestine, physical distention increases firing of stretch-sensitive vagal afferents. In addition, chemodetection of food by intestinal endocrine cells stimulates secretion of hormones such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY). These responses have three primary functions.

First, they cause contraction of the pyloric sphincter, a valve between the stomach and intestine. This limits further passage of food, preventing the small intestine from being overloaded. Second, the intestinal hormones stimulate secretion of bile and enzymes into the intestinal lumen to aid digestion. Third, the vagal afferents and the intestinal hormones decrease subsequent food intake, bringing about meal termination (satiation). The intestinal hormones accomplish this primarily by stimulating local vagal afferent terminals, which in turn excite neurons in the caudal region of the NTS.

Two of these hormones, GLP-1 and PYY, may also directly stimulate neurons in the brain. The activated neurons in the NTS project directly, or via a relay in the lateral parabrachial nucleus, to neurons in the forebrain, including the amygdala and hypothalamus. Neurons in the lateral parabrachial nucleus that express calcitonin gene-related polypeptide (CGRP) are one such important relay involved in satiation. These circuits then bring about meal termination.

When food is absorbed, the increase in blood glucose stimulates β-cells to release insulin and the hormone amylin. Amylin then excites neurons in the area postrema (a circumventricular organ outside the blood–brain barrier, located just above the NTS).

Circulating amylin increases within minutes following a meal, decreasing subsequent food intake.

Ghrelin is released by endocrine cells in the stomach. Unlike the factors described above, its secretion is high before eating and falls during the meal. It may play a role in meal initiation. Indeed, ghrelin is the only known systemic factor that increases hunger and thus eating. It excites neurons in a number of sites, including agouti-related peptide neurons in the arcuate nucleus (see below). The physiological significance of ghrelin is unclear because deletion of its gene does not appear to affect hunger.

*Blood Glucose and Insulin Affect Appetite.* Glucose is sensed by neurons in the periphery, hindbrain, and hypothalamus. Although glucose sensing does not appear to play a role in the day-to-day regulation of energy balance, the detection of and response to dangerously low blood glucose levels (*glucopenia*) is an important function of the brain. Two adaptive responses are initiated: (1) intense glucoprivic hunger, due at least in part to indirect activation of agouti-related peptide neurons, and (2) secretion of glucagon, epinephrine, and corticosteroids, which stimulate hepatic glucose production. The hormonal responses are caused by increases in sympathetic outflow as well as activation of the CRH pathway associated with stress (Chapter 61). Amino acids also can be sensed and, consequently, regulate energy balance and dietary choice—the latter to ensure ingestion of sufficient quantity and quality of protein.

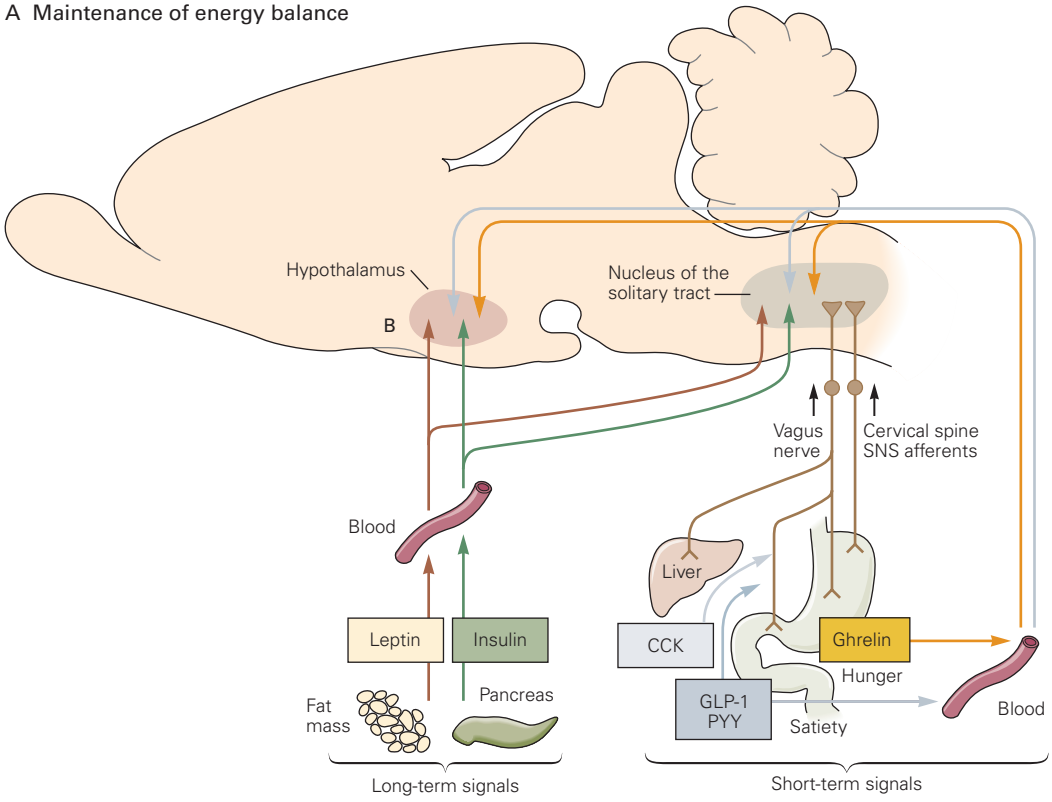
Insulin, on the other hand, is thought to signal an increase in fat stores. Insulin's primary function is to control blood glucose, the stimulus for its secretion. Insulin lowers blood glucose by driving it into muscle and fat cells and by decreasing its production by the liver. As fat stores increase, its ability to do this is decreased (a phenomenon called insulin resistance). Thus, higher fat stores increase basal and meal-stimulated insulin secretion in an effort to overcome resistance and normalize glucose. The fat store–mediated increase in insulin levels inhibits neurons in the hypothalamus, especially the arcuate nucleus, which is thought to decrease hunger.

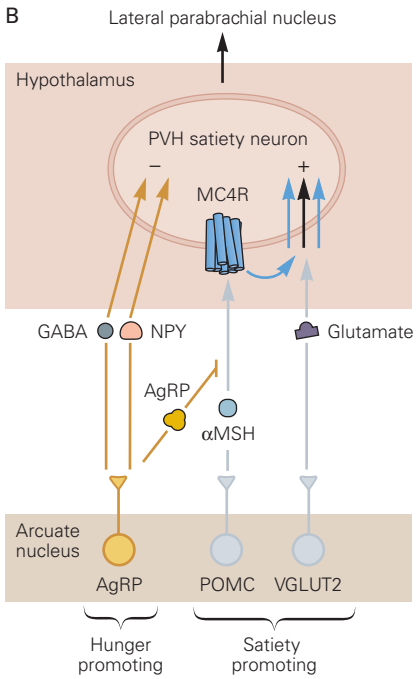
*The Fat Cell Hormone Leptin Signals the Brain About Fat Stores and Affects Hunger and Energy Expenditure.* In 1949, scientists at the Jackson Laboratory in Maine noted the appearance of "some very plump young mice." This obesity was due to a genetic mutation, which they named *obese* (*ob*). Sixteen years later, they identified another obesity mutation, *diabetes* (*db*). The extreme obesity of *ob/ob* and *db/db* mice results from intense hyperphagia and reduced brown fat thermogenesis. Based on a series of parabiosis experiments, Douglas Coleman proposed that *ob/ob* mice lack a circulating satiety factor and that *db/db* mice lack its receptor.

In a tour-de-force positional cloning effort led by Jeffrey Friedman and Rudolph Leibel, the *ob* gene was localized on a small region on chromosome 6. Friedman and his lab then homed in on and identified the *ob* gene. Renamed the *leptin* gene, it encodes leptin, a 167-amino acid protein secreted by adipocytes in proportion to the size of fat stores. Treating *ob/ob* mice with leptin cures their obesity. The *db* gene was identified a few years later, and as predicted by Coleman, it turned out to encode leptin's receptor and was found to be expressed by neurons in the hypothalamus. It is an interleukin-6–type class I cytokine receptor that produces its antiobesity effects by activating the JAK2/STAT3 signaling pathway.

Much has been learned subsequently about leptin. First, humans with a genetic deficiency of leptin or its receptor, like the mutant mice, are massively obese; hence, leptin's function is highly conserved, and such mutations are extremely rare. Second, humans with common forms of obesity have very high circulating levels of leptin, a by-product of their increased fat stores. This finding initially led to the view, later questioned, that "garden variety" obesity is caused by resistance to leptin action. Third, starvation, which reduces fat stores, drastically decreases leptin levels. This reduction is of interest because fasting causes many adaptive responses that are also seen in mice and humans that lack leptin: hunger, low energy expenditure, decreased fertility, and other altered neuroendocrine responses. Indeed, restoration of normal leptin levels in fasted individuals reverses or ameliorates many of fasting's effects. Thus, leptin's primary function is to signal, when its levels are low, that fat stores are inadequate.

These low leptin levels then bring about key adaptive responses such as increased hunger, decreased sympathetically mediated thermogenesis (to conserve limited fuel stores), decreased fertility (to prevent pregnancy when its demands cannot be met), and others. According to this view, leptin's dynamic range for signaling extends from the very low levels seen with fasting, signaling that fat stores are too low, to the levels found in well-fed, nonobese individuals, signaling that fat stores are sufficient. Levels above this may produce some effect to restrain obesity, but this effect, if present, is remarkably weak. Thus, the defense of energy balance is asymmetric—strong against low stores, weak against high stores. A corollary of this is that obese individuals do not have leptin resistance;


A Maintenance of energy balance
Hypothalamus
B
Nucleus of the solitary tract
Vagus nerve
Cervical spine SNS afferents
Blood
Liver
Leptin
Insulin
CCK
Ghrelin
Hunger
GLP-1 PYY
Satiety
Blood
Fat mass
Pancreas
Long-term signals
Short-term signals


B
Lateral parabrachial nucleus
Hypothalamus
PVH satiety neuron
–
+
MC4R
GABA
NPY
Glutamate
AgRP
αMSH
Arcuate nucleus
AgRP
POMC
VGLUT2
Hunger promoting
Satiety promoting