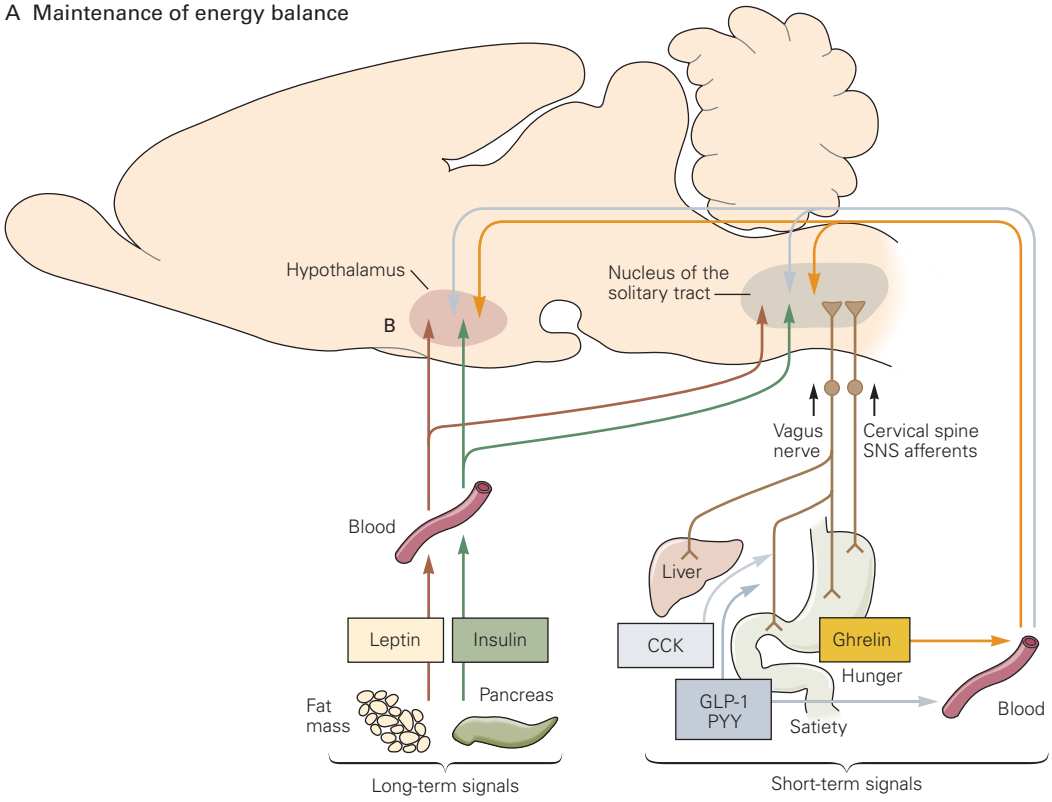
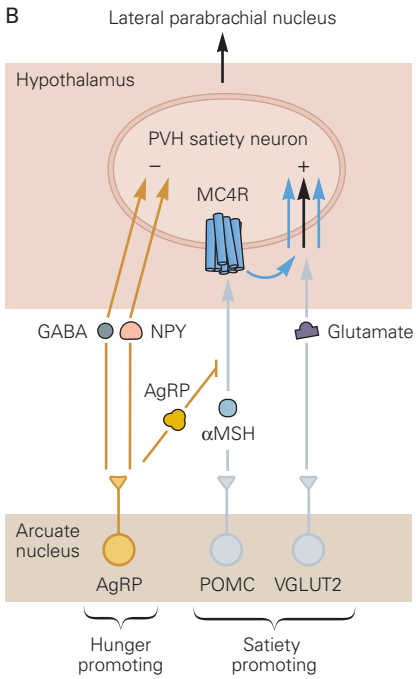

A Maintenance of energy balance
Hypothalamus
B
Nucleus of the solitary tract
Vagus nerve
Cervical spine SNS afferents
Blood
Liver
Leptin
Insulin
CCK
Ghrelin
Hunger
GLP-1 PYY
Satiety
Blood
Fat mass
Pancreas
Long-term signals
Short-term signals


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

rather, they simply have leptin levels that exceed the maximally effective concentration.

POMC, AgRP, and MC4R Neurons Are Key Nodes in the Afferent/Efferent Loop

Neuron-specific manipulation technologies have revealed two antagonistic populations of neurons in the arcuate nucleus that control energy balance: one expresses agouti-related peptide (AgRP) and the other the precursor polypeptide proopiomelanocortin (POMC) (Figure 41–14B). POMC neurons decrease hunger and stimulate sympathetically driven energy expenditure; AgRP neurons do the opposite. POMC neurons release the processed peptide α-melanocyte-stimulating hormone (αMSH), which activates the melanocortin-4 receptor (MC4R), a G protein–coupled receptor.

The downstream MC4R-expressing neurons that control hunger lie within the PVH. When these MC4R neurons are excited by αMSH released from POMC afferents, hunger is decreased. The PVH-MC4R "satiety neurons" are glutamatergic; they decrease hunger via their excitatory projections to the lateral parabrachial nucleus.

The MC4R-expressing neurons that control energy expenditure are sympathetic preganglionic neurons in the spinal cord. POMC neurons project to these sites, in addition to the PVH, increasing sympathetically driven energy expenditure.

The AgRP neurons increase hunger in part by opposing the actions of POMC neurons (Figure 41–14B). They release three factors: AgRP, an inverse agonist of MC4R, and neuropeptide Y and γ-aminobutyric acid (GABA), two inhibitory transmitters. The AgRP neurons project to and inhibit the PVH-MC4R satiety neurons and directly inhibit POMC neurons. In addition, different subsets of arcuate AgRP neurons project to other sites, including the lateral hypothalamus and the bed nucleus of the stria terminalis. These sites, when inhibited by AgRP inputs, can also stimulate hunger.

A third group of neurons in the arcuate nucleus express VGLUT2, release glutamate, and act in parallel with POMC neurons to induce satiety (Figure 41–14B). Like POMC neurons, and opposite to AgRP neurons, they excite the PVH-MC4R satiety neurons. αMSH/MC4R signaling in PVH-MC4R neurons causes satiety by two mechanisms: by directly activating the PVH-MC4R satiety neurons and by upregulating excitatory transmission from the VGLUT2 neurons to the PVH-MC4R neurons via postsynaptic facilitation.

The importance of the POMC, AgRP, and PVH-MC4R satiety neurons in regulating food intake is supported by a number of compelling findings. First, fasting activates AgRP neurons and inhibits POMC neurons, while feeding or leptin treatment does the opposite. The downstream PVH-MC4R satiety neurons are inhibited by fasting and excited by feeding. Second, genetic deficiency of the POMC protein or MC4R causes massive obesity. Third, genetic ablation of AgRP neurons in mice causes starvation, while stimulation of AgRP neurons rapidly brings about extreme hyperphagia, even in mice that are calorically replete and otherwise sated. Finally, several findings implicate the PVH-MC4R satiety neurons as an important

Figure 41–14 (Opposite) Neural and endocrine components combine to regulate energy balance.

A. *Short-term signals*. During meals, cholecystokinin (**CCK**) from the intestinal tract stimulates sensory fibers of the vagus nerve, thus promoting satiation (meal termination). Glucagon-like peptide-1 (**GLP-1**) and peptide YY (**PYY**), also released by the intestinal tract, appear to work on both sensory fibers of the vagus and neurons in the brain. The vagal sensory fibers, along with sympathetic fibers from the gut and orosensory information, converge in the nucleus of the solitary tract (NTS). Prior to mealtime, release of ghrelin from the stomach peaks, providing a blood-borne signal to neurons in the brain. Whereas CCK promotes satiety, ghrelin promotes eating.

Long-term signals. Leptin and insulin are among the humoral signals that inform the brain about the status of the fat stores. Leptin is produced in fat-storing cells, whereas insulin is produced in the pancreas. Both hormones are sensed by receptors in the arcuate nucleus of the hypothalamus as well as by receptors in the NTS. Leptin and insulin reduce food intake and increase energy expenditure. (Abbreviation: **SNS**, sympathetic nervous system.)

B. Neurons in the arcuate nucleus that synthesize agouti-related peptide (**AgRP**), proopiomelanocortin (**POMC**), and vesicular glutamate transporter 2 (**VGLUT2**) project to the paraventricular nucleus of the hypothalamus (**PVH**) where they control hunger and satiety. Satiety-promoting POMC neurons release the processed POMC peptide, α-melanocyte stimulating hormone (**αMSH**), which binds to melanocortin-4 receptors (**MC4R**) on neurons in the PVH. Activation of these neurons causes satiety. In contrast, the hunger-promoting AgRP neurons release two inhibitory transmitters, γ-aminobutyric acid (**GABA**) and neuropeptide Y (**NPY**), and the MC4R antagonist AgRP. Their combined effect is to inhibit the MC4R-expressing neurons, causing hunger. The MC4R-expressing neurons also receive direct excitatory input from another population of arcuate neurons, VGLUT2 neurons, which also promote satiety. The binding of αMSH to MC4R causes satiety by two mechanisms: by directly activating the PVH-MC4R neurons and by upregulating excitatory transmission from the arcuate VGLUT2 neurons to the PVH-MC4R neurons (**blue arrows**). Finally, PVH-MC4R neurons project to the lateral parabrachial nucleus where they promote satiety.

downstream target of AgRP and POMC neurons. Most notable are the development of marked hyperphagia and obesity in mice genetically engineered to lack MC4R neurons in the PVH and the induction of intense feeding following optogenetic stimulation of AgRP terminals in the PVH, which inhibits the satiety neurons.

Surprisingly, environmental cues that predict future ingestion of food induce inhibition of AgRP neurons. Indeed, in fasted mice, which have high AgRP neuron activity, presentation of food alone without ingestion decreases AgRP neuron firing. This is roughly analogous to rapid, feedforward inhibition of vasopressin secretion and thirst neuron activity (mentioned previously). Thus, in addition to receiving strong bottom-up feedback signals from the body, the hunger-promoting AgRP neurons also receive top-down feedforward information from the environment. The function of this input is not yet clear, but it could serve as an anticipatory signal to limit future ingestion of excessive calories, or as discussed below, it could serve as a reward-related signal to motivate feeding.

Finally, the complete pathway accounting for regulation of hunger by the AgRP and POMC neuron → PVH pathway is presently unknown. It is likely that, via relays through a number of synapses, it affects neuronal activity in pathways controlling reward as well as perception. This is the case because, in the fasted state, food and cues predictive of food are both more rewarding and much more likely to become the focus of attention. How specificity for a given goal—in this case food—is retained as neural information flows from the highly specific deficiency-regulated homeostatic neurons in the hypothalamus to the "nonspecific" reward and perception pathways in the accumbens and cortex is one of the great mysteries of motivated behaviors such as hunger and thirst. The solution could provide clues for disorders of motivated behavior like drug addiction.

Psychological Concepts Are Used to Explain Motivational Drives Such as Hunger

In a simplified stimulus–response view of behavior, one might assume that neural detection of water or energy deficiency (the stimulus) is hardwired to motor pathways for drinking or eating (the response), and thus analogous to the knee-jerk stretch reflex (Chapter 3). However, this cannot be the case because the responses that can be employed to obtain food, all motivated by the deficiency stimulus, are remarkably varied and complex—to such a degree that they could not be hardwired. Indeed, animals can complete an infinite number of complex operant learning tasks to obtain water or food rewards.

The challenge to understanding motivational drive is to devise a model that accounts for the ability of deprivation states to induce behavior that is remarkably varied and complex, while remaining completely specific for one goal. Two compelling theories are relevant. According to *incentive motivation theory*, deficiency increases the reward value of food and water. *Drive reduction theory* posits that deficiency generates an aversive state, the resolution of which is thought to motivate behavior. Notably, these two views are not mutually exclusive and may in some ways be two sides of the same coin.

Incentive Motivation: Fasting Increases the Reward Value of Food. The incentive motivation theory is the work of theorists over many years, most recently refined by Frederick Toates and Kent Berridge. Consider eating and the hunger drive. Briefly, food is viewed as inherently rewarding. Through learned associations, cues and tasks related to obtaining food also become rewarding; in this way, varied and complex behavioral responses are learned (Figure 41–15A).

The theory posits that the deprivation state increases the reward value of food and of the related cues and tasks (ie, their incentive salience). Thus, during fasting, the reward value is increased, and all food and cues and tasks related to food are extremely rewarding. After a meal, the reward value is decreased, and only the most inherently palatable foods, for example, ice cream, are still sufficiently rewarding to be eaten. The task of neuroscientists is to determine how deprivation increases reward value. Experimental activation of AgRP neurons in an otherwise sated mouse dramatically increases the reward value of food—remarkably, the reward value of food is increased to the same extremely high level seen with fasting.

Drive Reduction: Activity of AgRP Hunger Neurons Can Be Aversive. As we know from personal experience, the behavioral states created by dehydration and caloric deficiency, namely thirst and hunger, are unpleasant. It was originally proposed many years ago that reduction of these states, which relieves this discomfort, is rewarding and hence motivates drinking and feeding. Recently, Scott Sternson's group has provided compelling new support for a modified version of this model (Figure 41–15B). Using a behavioral conditioning paradigm such as the place preference test, they discovered that optogenetic activation of AgRP neurons in sated mice was aversive. When the same mice were then studied in a food-deprived state (which is associated with

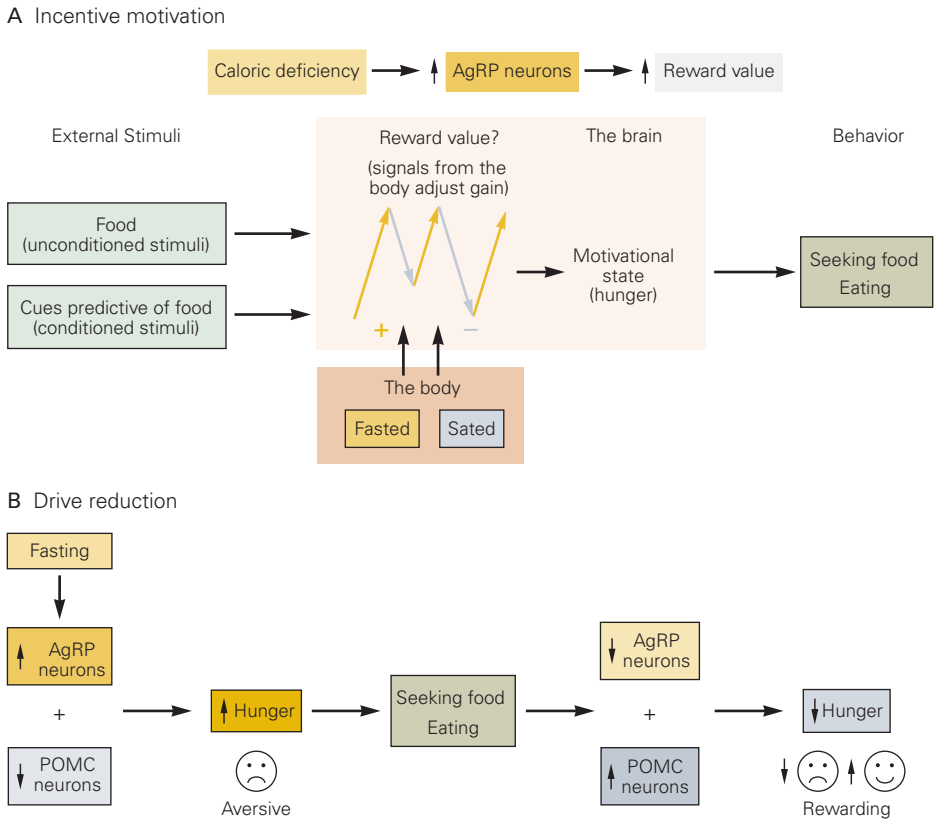


Figure 41–15 Two theories of how fasting promotes eating.

A. *Incentive motivation.* Food is inherently rewarding, and different foods have different reward values (lettuce–low, ice cream–high). Through learned associations, cues that predict food become rewarding. The fed (sated) versus fasted state sets the gain determining how rewarding food and food cues are. Fasting greatly increases while the sated state decreases reward value.

B. *Drive reduction.* The feeling of hunger is aversive. Eating reduces this aversive state. Consistent with this theory, experimental stimulation of hunger-promoting agouti-related peptide (**AgRP**) neurons is aversive, while stimulation of satiety-promoting paraventricular nucleus of the hypothalamus melanocortin-4 receptors (**MC4R**) neurons (which are downstream of the AgRP and proopiomelanocortin [**POMC**] neurons) in an otherwise hungry mouse creates a pleasant feeling.

increased AgRP neuron activity), they engaged in behaviors that in the earlier conditioning had lowered AgRP neuron activity—in short, they acted as if motivated to turn off the AgRP neuron–induced aversive state. Similar results were obtained with thirst neurons in the SFO.

In further support of this view, optogenetic activation of downstream PVH-MC4R satiety neurons in calorically deprived mice, but not in sated mice, is emotionally positive (ie, the mice like it). Thus, causing satiety when otherwise hungry is pleasant. In total, these findings provide strong evidence for the view that homeostatic deficiency is unpleasant, that the aversive state is caused by activation of deficiency-responsive homeostatic neurons, and that when afflicted by the deficiency-induced aversive state animals engage in behaviors that they associate with relief.

This model provides an explanation for why dieting is so difficult. It generates an aversive, unpleasant state that can only be relieved by eating. Finally, the rapid reduction in AgRP neuron activity in response to sensory cues that predict food, and the alleviation of the aversive state that this should cause, could function as a rewarding "teaching signal" that motivates pursuit of the goal (food).

Sexually Dimorphic Regions in the Hypothalamus Control Sex, Aggression, and Parenting

Now we turn to behaviors that are not homeostatic, but are controlled by the hypothalamus, involve integration between sensory cues and signals from the body (ie, gonadal steroids), and are critical for survival of the species.

Males and females differ in their sexual, aggressive, and parenting behaviors. These differences are especially notable in animals, for example in mice, where they are clearly hardwired (ie, require no prior training). These differences include mounting and lordosis by males and females, respectively; territorial-related behaviors such as marking and aggression by males; and the tendency toward nurturing in females versus aggressive behavior in males when dealing with the young. The latent capacity for these sexually dimorphic behaviors is the product of sex steroid action on the brain during embryogenesis (Chapter 51). Full actualization of adult sex-specific behaviors also requires adult levels of gonadal steroids. Sex chromosome–specific genes, other than *Sry*, which causes male sex determination, as well as genes that are imprinted in a sexually dimorphic way, also subtly modulate sex-specific behaviors independent of gonadal steroids. Ultimately, the behaviors themselves are triggered by cues from the environment, such as pheromones.

Two regions of the hypothalamus are critically involved in the control of these behaviors, the POA and the ventral lateral aspect of the ventromedial hypothalamic nucleus (vlVMH). Both sites are sexually dimorphic: The POA contains more neurons in males, and the vlVMH contains more progesterone-expressing neurons in females. These sites are heavily interconnected, and they receive strong input from two other sexually dimorphic areas outside the hypothalamus: the medial division of the posteromedial bed nucleus of the stria terminalis (BNSTmpm) and medial amygdala (MeA).

Sexual Behavior and Aggression Are Controlled by the Preoptic Hypothalamic Area and a Subarea of the Ventromedial Hypothalamic Nucleus

Brain lesion studies have demonstrated that the sexually dimorphic brain regions—the accessory olfactory bulb, BNSTmpm, MeA, and particularly POA and vlVMH—play important roles in sex-specific behaviors. Neurons in these regions are highly interconnected, are downstream of pathways involved in detecting and responding to pheromones (BNSTmpm and MeA), express sex hormone receptors, and, with the exception of neurons in the vlVMH, also express aromatase (Figure 41–16). Neurons in both the POA and vlVMH send strong projections to the lateral periaqueductal gray area, which is thought to mediate and coordinate the motor and autonomic aspects of sexual and aggressive behavior.

The vlVMH plays a critical role in controlling sexually dimorphic behaviors. Firing rates of vlVMH neurons in male mice increase during mating or periods of aggression toward a male intruder. Stimulation of these neurons triggers intense attack behavior toward intruder males and toward atypical targets for male aggression such as castrated males, females, or even rubber gloves! Silencing these neurons eliminates aggressive behavior toward male intruders.

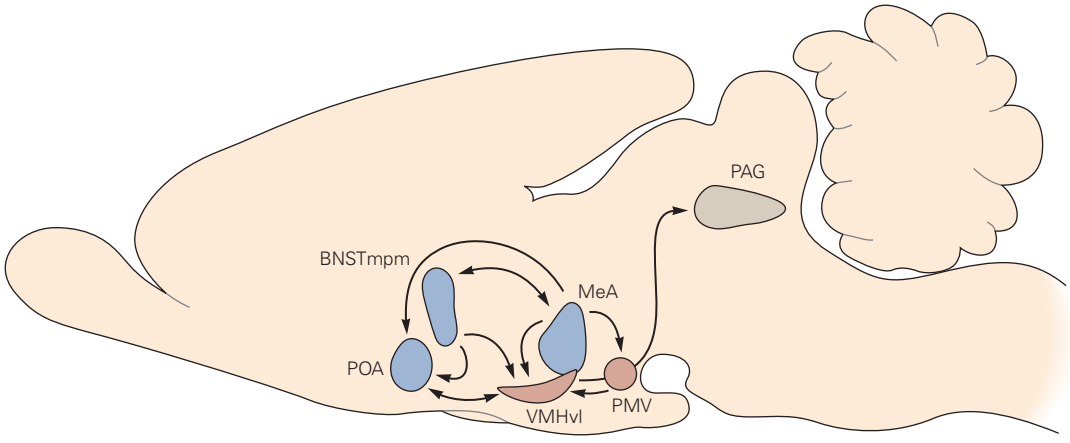


Figure 41–16 Sexually dimorphic neural structures comprise highly interconnected behavioral circuits. Hypothalamic and amygdalar nuclei that regulate sexually dimorphic behaviors are extensively interconnected. These areas process pheromonal information, and subsets of adult neurons within each of these regions express sex hormone receptors; neurons within some of these regions (**blue**) also express aromatase. (Abbreviations: **BNSTmpm**, medial division of the posteromedial bed nucleus of the stria terminalis; **MeA**, medial amygdala; **PAG**, periaqueductal gray; **PMV**, ventral premammillary nucleus; **POA**, preoptic hypothalamus; **VMHvl**, ventrolateral component of the ventromedial hypothalamus.) (Reproduced, with permission, from Yang and Shah 2014. Copyright © 2014 Elsevier Inc.)

Furthermore, stimulation of a subset of vlVMH neurons that express estrogen receptor evokes either sexual behavior (mounting) or aggression, depending on the number of neurons activated and their degree of activation: Lower levels of activation induce mounting, whereas higher levels induce aggression. Consistent with these results, genetic ablation of related progesterone receptor–expressing vlVMH neurons causes loss of both sexual behavior and aggression in males and loss of sexual behavior in females. Thus, it is clear that sex neurons in the vlVMH-expressing steroid receptors play a critical role in driving sexual behavior in males and females and aggression in males.

Parental Behavior Is Controlled by the Preoptic Hypothalamic Area

Nurturing parental behavior is key to the survival of one's offspring. Male rodents demonstrate strikingly different patterns of behavior. Males can be nurturing or hostile to offspring, even to the point of infanticide, depending on whether they view the offspring as their own or those of another male. Female mice, on the other hand, are generally nurturing.

Social interaction between mouse pups and appropriately receptive adult female and male mice, but not hostile adult male mice, induces activity in subsets of galanin-expressing neurons in the POA. These offspring-activated neurons are largely distinct from POA neurons activated by mating. Genetic ablation of galanin-expressing POA neurons prevents nurturing parental behavior, even to the point of inducing uncharacteristic aggression in females toward their offspring. On the other hand, stimulation of these galanin-positive neurons in males, which are normally extremely hostile to unrelated pups, decreases aggression and induces nurturing pup grooming. Thus, neurons in the POA, in addition to controlling sexual behavior itself, also play a role in ensuring survival of the fruit of sexual behavior.

Highlights

1. The hypothalamus and the autonomic and neuroendocrine motor systems coordinate and control body homeostasis by inducing adaptive behaviors; by controlling glands, smooth muscle, cardiac muscle, and adipocytes; and by releasing hormones from the pituitary gland.
2. Homeostatic control of body temperature, fluid and electrolyte balance, and blood pressure allows organisms to function under harsh environmental conditions.
3. Feedback loops that sense temperature, osmolarity, blood pressure, and body fat are essential for homeostatic control. The combined action of multiple feedback-informed sensory-afferent/efferent-effector control loops results in emergent settling points.
4. Modality-specific hypothalamic neurons link specific interoceptive sensory feedback with outputs that control adaptive behaviors and physiologic responses. In addition to feedback, these modality-specific neurons also receive feedforward information regarding future anticipated homeostatic challenges.
5. The autonomic motor system contains neurons located in sympathetic, parasympathetic, and enteric ganglia located near the spinal column or embedded within peripheral targets. Functional subsets of autonomic neurons selectively innervate effector tissues comprised of smooth muscle, cardiac muscle, glandular epithelia, and adipocytes.
6. Sympathetic neurons are activated in response to exercise and stress. Parasympathetic and sympathetic neurons generally have antagonistic functions, but often act in concert. The enteric system coordinates peristaltic contractions of the gastrointestinal tract with mucosal function and local blood flow.
7. Preganglionic neurons that control the sympathetic and parasympathetic outflows are located in the spinal cord and brain stem.
8. Acetylcholine, norepinephrine, and neuropeptide cotransmitters act as synaptic signaling molecules in the autonomic motor system. Excitatory fast synaptic transmission in autonomic ganglia is mediated by acetylcholine acting on nicotinic receptors. G protein–coupled receptors in ganglia mediate additional pre- and postsynaptic excitatory and inhibitory effects. G protein–coupled receptors mediate transmitter actions at autonomic neuroeffector junctions.
9. The neuroendocrine system links the hypothalamus, via the pituitary gland, to various physiologic responses in the body. The posterior pituitary contains hypothalamic axon terminals that release two neurohormones into the blood: Vasopressin stimulates water reabsorption by the kidney, while oxytocin controls uterine contraction and milk release. The anterior pituitary contains endocrine cells that secrete hormones in response to factors released by hypothalamic neurons. These anterior pituitary hormones control the thyroid gland, glucocorticoid secretion

by the adrenal cortex, sex steroid secretion by the gonads, lactation, and linear growth.

10. Body temperature is detected in multiple sites including the periphery, in and around major organs, and in the brain. Constancy of body temperature is maintained by multiple thermoreceptor-afferent/thermoeffector-efferent control loops.
11. Some neurons in the lamina terminalis are activated by both dehydration and loss of intravascular volume. Key parameters sensed in these deficiency states include osmolarity and angiotensin II levels, respectively. When these neurons are activated, they cause thirst and release of vasopressin from the posterior pituitary. Vasopressin release is also rapidly regulated in a feedforward fashion by cues that anticipate future disturbances in osmolarity.
12. Energy balance involves short-term and long-term feedback signals. Short-term signals from the gut mediate satiation, which terminates meals. CCK, released by intestinal endocrine cells, plays a key role in satiation. A key long-term signal is leptin, which is secreted by adipocytes in proportion to the amount of fat stores. When fat stores are low, the consequent low levels of leptin signal the brain to induce a hunger state and to decrease energy expenditure, resulting in replenished fat stores.
13. Leptin is more effective in defending against low fat stores than in resisting obesity.
14. POMC-, AgRP-, and MC4R-expressing neurons in the hypothalamus are key nodes in the afferent/efferent loop controlling energy balance. Neurons that signal satiety are activated by satiety-promoting POMC neurons and inhibited by hunger-promoting AgRP neurons.
15. How specificity for a given goal (eg, food) is retained as neural information flows from the highly specific deficiency-regulated homeostatic neurons in the hypothalamus to the "nonspecific" reward and perception pathways in the accumbens and cortex is one of the great mysteries of motivated behaviors such as hunger and thirst. Solving this could provide clues for disorders of motivated behavior like drug addiction.
16. Leptin regulates hunger and energy expenditure in part by activating POMC neurons and inhibiting AgRP neurons. Hunger-promoting AgRP neurons are also rapidly regulated in a feedforward fashion by cues that anticipate future changes in energy balance.
17. Motivational drives such as hunger have been explained by two mechanisms: The deficiency state (starvation) increases the reward value of food, or deficiency generates an aversive state, the resolution of which motivates behavior.
18. Sexually dimorphic regions in the hypothalamus control sexual behavior and aggression. Neural activity in the sexually dimorphic preoptic area controls parental behavior. Full actualization of adult sex-specific behaviors also requires adult levels of gonadal steroids.

Bradford B. Lowell
Larry W. Swanson
John P. Horn

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