# 8.6 Energy Balance and Regulation of Food Intake

## Learning Objectives

- Describe a whole-body calorimeter
- Describe a bomb calorimeter
- List the Atwater factors
- Be able to use the Atwater factors to calculate the energy content of food
- Describe indirect calorimetry
- Use the volume of $O_2$ consumed, $CO_2$ produced, and urinary nitrogen to calculate the proteins, carbohydrates, and fats that are burned
- Use allometric formulas to estimate BMR
- Give subjective evidence that body weight is homeostatically regulated
- Distinguish between satiety signals and adiposity signals in regulation of food intake
- Identify the satiety center and the "feeding center" and why they are so designated
- List short-term signals that regulate food intake
- List long-term signals that regulate food intake
- Identify the following abbreviations for neurotransmitters involved in food regulation: POM, CART, AgRP, CCK, NPY
- Describe what is meant by a "glucose stat" and distinguish between glucose-sensitive and glucose-responsive neurons
- Indicate the part of the brain where food intake signals are integrated with hormonal signals

## EARLY STUDIES ON ENERGY BALANCE USED CALORIMETERS

The scientific foundations of nutrition began in the 1780s when Antoine Lavoisier and Simon Pierre de Laplace measured oxygen consumption and carbon dioxide production in humans and found that both increased after a meal and during exercise, even though the temperature of the subject did not change. They constructed a small calorimeter for guinea pigs and showed a direct relationship between heat given off by the animal and the respiratory exchange. These early experiments were improved upon by Atwater and colleagues, who constructed a calorimeter large enough for humans (see Figure 8.6.1). A summary of one of his experiments is shown in Table 8.6.1.

These results showed, within experimental error, that man was not an exception to the laws of thermodynamics. Man obeyed the conservation of energy law:

$$\text{Energy input} = \text{energy output} \quad [8.6.1]$$

This equation can be expanded to give

$$\text{Energy content of food} = \text{work output} + \text{net heat output} + \text{net storage} \quad [8.6.2]$$

This equation clarifies what is necessary to cause a negative storage of energy (a loss of body stores): either reduce the energy content of the food consumed or increase the work or heat output. Translated into clinical practice, this means that if you want to lose weight you must eat less or move more. Although this is conceptually easy, it is complicated by several facts: net heat output is related to the energy content of the food and the work output; and heat output is regulated by fat stores, so that heat output declines when one tries to lose weight.

## "THE ENERGY CONTENT OF FOOD" IS ITS HEAT OF COMBUSTION

Atwater and others had to determine the energy content of the food consumed by their experimental subjects. They did this using a bomb calorimeter, shown in Figure 8.6.2. Passing a small electric current ignites the food sample in the presence of high oxygen tension, which causes the organic material to burn. The chemical reactions are similar to those occurring in the body, except in the body the reactions occur at lower temperatures through enzyme-catalyzed reactions. The human body is capable of completely oxidizing carbohydrates and fats, but we only partially oxidize proteins, excreting urea as a waste product. Therefore, the energy of combustion of proteins in the bomb calorimeter exceeds that in the body by the amount of chemical energy stored in the waste urea. Atwater used these facts to derive the **Atwater factors**, which are still widely used today along with tables of food composition to calculate the energy content of specific foods (see Table 8.6.2). These factors make allowance for the energy lost in feces and in urine. They represent physiological approximations based on experiments with a limited number of subjects. In food tables, the protein content is usually obtained from the nitrogen content by multiplying by 6.25 (because most proteins




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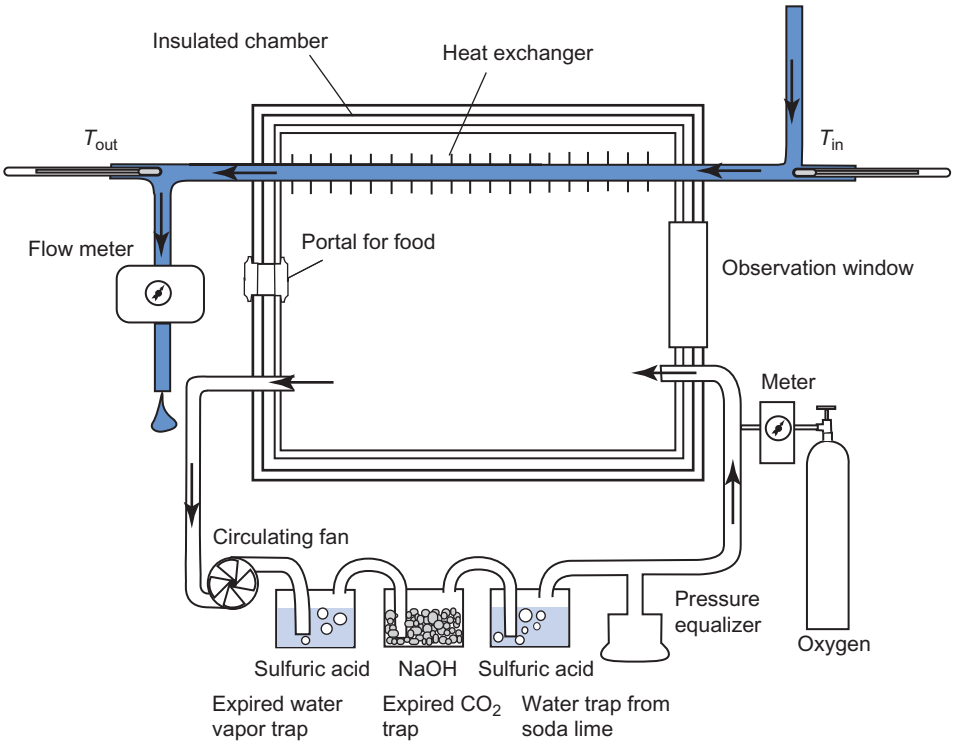


**FIGURE 8.6.1** The Atwater–Benedict respiration calorimeter. The chamber was thermally insulated from its surroundings. The heat produced by the person contained in the calorimeter was estimated from the temperature of the incoming water ($T_{in}$), the temperature of the water exiting the chamber ($T_{out}$), and the rate of water flow. Air was circulated by a blower. The air that left the chamber was scrubbed of water by passing it through sulfuric acid. A solution of NaOH or soda lime pellets absorbed the $CO_2$ produced. Known quantities of $O_2$ could be added to the air before it reentered the chamber. The amount of $CO_2$ produced could be estimated from the gain in weight of the soda lime.

**TABLE 8.6.1** Results from an Experiment by Atwater and Benedict 1899, in MJ

| Source of Energy | Total 4 Days | Average per Day |
|---|---|---|
| (a) Heat of combustion of food eaten | 41.22 | 10.31 |
| (b) Heat of combustion of feces | 1.26 | 0.32 |
| (c) Heat of combustion of urine | 2.25 | 0.56 |
| (d) Heat of combustion of alcohol | 0.35 | 0.09 |
| (e) Heat of protein gained "+" or lost "−" | −1.16 | −0.29 |
| (f) Heat of fat gained "+" or lost "−" | −2.26 | −0.56 |
| (g) Energy of food oxidized: $a-(b+c+d+e+f)$ | 40.78 | 10.19 |
| (h) Heat determined by calorimetry | 40.06 | 10.02 |
| (i) Difference more "+" or less "−" than g | −0.68 | −0.17 |
| (j) Difference (%) | −1.6 | −1.6 |

are typically 16% nitrogen by mass). However, this factor is too high for cereals and too low for milk (5.7 is better for cereals, 6.4 for milk).

The units for the Atwater factors are kcal $g^{-1}$. The **calorie** is the amount of heat energy necessary to warm 1 g of water from 14.5°C to 15.5°C. The **kcal** is often written as **Calorie**, which is a source of endless confusion. J. Joule (1818–1889) showed the equivalence of mechanical, electrical, and heat energy. The joule is a N m ($=kg\,m^2\,s^{-2}$) or a volt-coulomb. The conversion factors are as follows:

$$1\ cal = 4.184\ J \quad 1\ J = 0.239\ cal$$

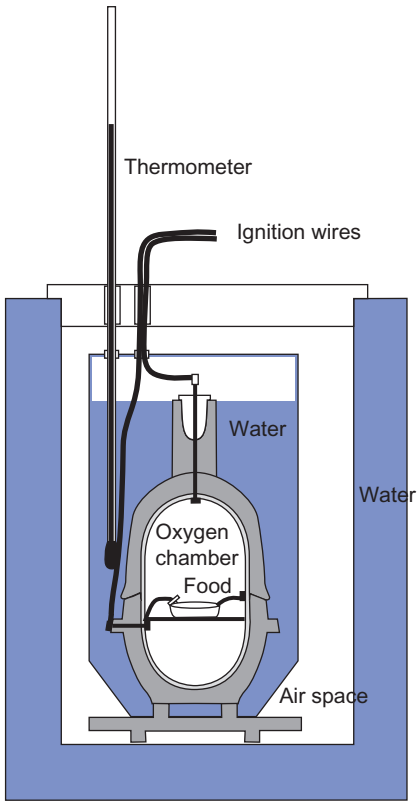


**FIGURE 8.6.2** A bomb calorimeter. A sample of food is placed in a crucible within a steel-walled vessel containing a high oxygen tension. Passing a current ignites the food, combining it with the oxygen and producing heat from the oxidation reaction. The heat produced is determined by measuring the temperature increase in the water surrounding the calorimeter. The calorimeter is calibrated in advance to obtain a "calorimeter constant" that reflects the heat capacity of both the water and the metal of the calorimeter. Energy added by the electric current is calculated and subtracted from the heat produced.

**TABLE 8.6.2** The Atwater Factors and Their Derivation for Different Macronutrients

| Macronutrients | Bomb Calorimetry (kcal $g^{-1}$) | Urinary Loss (kcal $g^{-1}$) | Digestibility (%) | Atwater Factor (kcal $g^{-1}$) |
|---|---|---|---|---|
| Proteins | 5.65 | 1.25 | 92 | 4.0 |
| Carbohydrates | 4.1 | 0 | 99 | 4.0 |
| Fats | 9.4 | 0 | 95 | 9.0 |
| Alcohol | 7.1 | Trace | 100 | 7.0 |

**TABLE 8.6.3** Energy Yields from Oxidation of Substrates

| Substrate | $O_2$ Consumed | $CO_2$ Produced | RQ | Heat | | Energy Equivalents in Energy per Liter of $O_2$ | | Energy Equivalents in Energy per Liter of $CO_2$ | |
|---|---|---|---|---|---|---|---|---|---|
| | L $g^{-1}$ | L $g^{-1}$ | | kJ | kcal | kJ | kcal | kJ | kcal |
| Starch | 0.829 | 0.829 | 1.00 | 17.6 | 4.20 | 21.2 | 5.06 | 21.2 | 5.06 |
| Sucrose | 0.786 | 0.786 | 1.00 | 16.6 | 3.96 | 21.1 | 5.04 | 21.1 | 5.04 |
| Glucose | 0.746 | 0.746 | 1.00 | 15.6 | 3.74 | 21.0 | 5.01 | 21.0 | 5.01 |
| Lipid | 2.019 | 1.427 | 0.71 | 39.6 | 9.46 | 19.6 | 4.69 | 27.7 | 6.63 |
| Protein | 1.010 | 0.844 | 0.83 | 19.7 | 4.70 | 19.0 | 4.66 | 23.3 | 5.58 |
| Lactic acid | 0.746 | 0.746 | 1.00 | 15.1 | 3.62 | 20.3 | 4.85 | 20.3 | 4.85 |

*Data from G. Livesey and E. Marinos,* Am. J. Clin. Nutr. ***47****:608–626, 1988.*

## MEASUREMENT OF ENERGY EXPENDITURE BY INDIRECT CALORIMETRY

The measurement of energy expenditure by measuring the heat dissipated by the body is called **direct calorimetry**. Direct calorimetry is technically difficult and tedious and subject to additive errors. Atwater found that the total energy expenditure is quantitatively related to the total oxygen consumption. Thus an indirect measure of energy expenditure can be accomplished by measuring gas exchange.

The **energy equivalence** of $O_2$ consumption for the three macronutrients was determined calorimetrically in 1897 by Zuntz in Switzerland, and much more recently as well. The recent results offer no substantial changes from the original data of Zuntz. The recent data are given in Table 8.6.3.

The theoretical energy equivalence of proteins is much harder to assess because of the mixture of amino acids that make up proteins—proteins are heterogeneous. However, the energy equivalence can be determined experimentally, as shown in Table 8.6.3. According to this table, the energy equivalence of oxygen is about 5.0 kcal $L^{-1}$ for carbohydrates, 4.7 kcal $L^{-1}$ for fats, and about 4.6 kcal $L^{-1}$ for proteins. Since we burn a mixture of these macronutrients, we can take an average of about 4.85 kcal $L^{-1}$ and estimate the total metabolic rate or energy consumption as

$$[8.6.3] \qquad \begin{aligned} M &= 4.85 \text{ kcal L}^{-1} \times Q_{O_2} \\ &= 20.3 \text{ kJ L}^{-1} \times Q_{O_2} \end{aligned}$$

### EXAMPLE 8.6.1 Calculate the Energy Equivalence of Carbohydrates and Fats

The complete oxidation of glucose is written as

$$[8.6.4] \qquad C_6H_{12}O_6 + 6O_2 \Rightarrow 6H_2O + 6CO_2 + \text{heat}$$

For every mole of glucose, 6 moles of oxygen are consumed and 6 moles of carbon dioxide are produced. Bomb calorimetry gives 3.73 kcal $g^{-1}$ of heat liberated or 671 kcal $mol^{-1}$ = 2807 kJ $mol^{-1}$. The 6 moles of $O_2$ at STPD (standard temperature, 0°C, and pressure, 1 atm = 760 mmHg, and dry) occupies approximately 134.4 L. Thus the energy equivalence of $O_2$ when glucose is burned is 671 kcal $mol^{-1}$/134.4 L $mol^{-1}$ = **4.99 kcal $L^{-1}$**.

The complete oxidation of tripalmitin is written as

$$[8.6.5] \qquad C_{51}H_{98}O_2 + 72.5O_2 \Rightarrow 49H_2O + 51CO_2 + \text{heat}$$

The heat of combustion for tripalmitin is 7415 kcal $mol^{-1}$, corresponding to the consumption of 72.5 moles of oxygen, for an energy equivalence of 7415 kcal $mol^{-1}$/1624 L $mol^{-1}$ = **4.56 kcal $L^{-1}$**.

where $Q_{O_2}$ is the rate of oxygen consumption in Liters at STPD per unit time and $M$ is the metabolic rate.

## INDIRECT CALORIMETRY AND URINARY NITROGEN ALLOW ESTIMATION OF CATABOLISM OF MACRONUTRIENTS

Suppose an individual oxidizes $c$ grams of glucose, $f$ grams of fat, and $p$ grams of proteins. The $p$ grams of protein will translate to 0.16 g of urinary nitrogen, $n$, because the only source of urinary nitrogen is protein catabolism, and proteins are nearly uniformly 16% nitrogen by mass. Thus the amount of protein being catabolized can be calculated directly from urinary nitrogen excretion as

[8.6.6] $$p = 6.25n$$

where $p$ is the grams of protein and $n$ is the grams of urinary nitrogen. According to the coefficients in Table 8.6.3, we can write the oxygen consumption as

[8.6.7] $$\begin{aligned} V_{O_2} &= 0.746c + 2.02f + 1.01p \\ V_{CO_2} &= 0.746c + 1.43f + 0.844p \end{aligned}$$

where $V_{O_2}$ and $V_{CO_2}$ are the volumes of $O_2$ consumed and $CO_2$ produced, respectively, at STPD. If we measure urinary nitrogen, we can calculate $p$ according to Eqn (8.6.6). If we measure the $O_2$ consumption and $CO_2$ production, we can calculate $c$ and $f$ by solving the simultaneous equations of Eqn (8.6.7).

## ENERGY EXPENDITURE CONSISTS OF BASAL METABOLISM PLUS ACTIVITY INCREMENT

The **basal metabolic rate, BMR**, is *defined* as **the metabolic rate during rest but while the person is awake**. The person should be in a postabsorptive state, not having eaten within the last 12 hours. The person should also not have strenuously exercised within the previous 12 hours. The air in the room should be comfortable with all sources of excitement removed. The BMR is usually determined by indirect calorimetry by measuring $Q_{O_2}$, the rate of oxygen consumption. The resting energy expenditure (REE) differs from the BMR in that the determination of the REE does not require fasting for 12 hours.

Body size, composition, age, and gender have marked effects on the BMR. The overall volume of the body increases approximately according to the cube of the linear dimensions, whereas the surface area increases according to the square. Thus larger people have a smaller surface area to volume ratio. Since body heat must be shed on the surface, this means that larger people must produce less heat per unit body dimension, or they will get too hot too easily. Max Rubner (1854–1932) showed in 1883 that mouse, dog, man, and horse had greatly different BMR when expressed per unit body weight, but they were all very similar when compared per unit surface area. Based on the geometric argument above, Rubner proposed that $BMR = KM^{2/3}$, where $M$ is the mass and $K$ is a constant. The exponent of 0.67 in Rubner's equation is the subject of some debate. Max Kleiber reevaluated the effect of body size on metabolism and found an exponent of 3/4 (actually 0.754). Although the absolute differences in these exponents (0.67 vs 0.75) does not seem large, much has been made of a 2/3 or 3/4 power law because it was thought to be one of the few unifying principles of biology that applied equally well to microorganisms as to elephants. It is likely that no single process determines either the preexponential or exponential factor in the allometric formula:

[8.6.8] $$BMR = aM^b$$

It is likely that herbivores have a different relationship between BMR and $M$ because of their extensive microbial activity and their nearly continuous state of feeding. Inclusion of herbivores in regressions of BMR against $M$ skews the curve.

## EMPIRICAL FORMULAS FOR BMR

Measurements of human BMR have been made as a function of age and body composition (see Figure 8.6.3). This gives the BMR in terms of kcal per square meter of surface per hour. By carefully measuring the surface area of a few persons (by covering them with tiny squares), researchers have derived an empirical equation for surface area. The DuBois–Meeh formula for surface area is

[8.6.9] $$BSA(m^2) = 0.007184 \times W(kg)^{0.245} \times H(cm)^{0.725}$$

where BSA is the **body surface area**, in $m^2$, $W$ is the weight, in kg, and $H$ is the height, in cm. These are empirical data obtained using only nine subjects and its

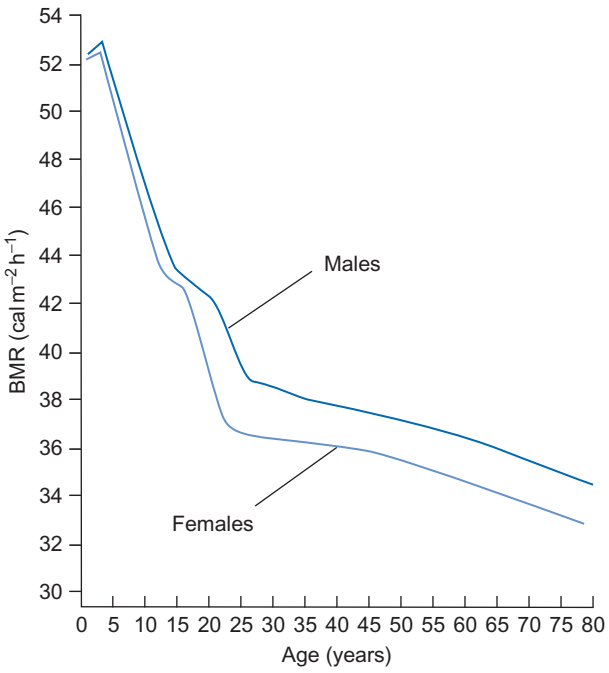


**FIGURE 8.6.3** Basal metabolic rate as a function of age in human females and males. The BMR is given here as the kilocalories of energy expenditure per square meter of body surface area, per hour.

use is debated. Harris and Benedict in 1919 developed an equation for predicting the BMR for men and women based on their weight, $W$, in kg, their height, $H$, in cm and their age, $A$, in years. The equation gives the BMR in **kcal per day**:

$$\text{Men BMR} = 66.5 + (13.7 \times W) + (5.0 \times H) - (6.8 \times A)$$
$$\text{Women BMR} = 655.1 + (9.56 \times W) + (1.85 \times H) - (4.7 \times A)$$
[8.6.10]

A more recent equation published by Mifflin and St. Jeor in 1990 gives the REE, in kcal per day, as

$$\text{Men REE} = 5 + (10 \times W) + (6.25 \times H) - (5 \times A)$$
$$\text{Women REE} = -161 + (10 \times W) + (6.25 \times H) - (5 \times A)$$
[8.6.11]

## EATING FOOD INCREASES METABOLISM

The metabolic response to the ingestion of food has been variously called "**diet-induced thermogenesis**," "**thermic effect of food**," "**specific dynamic action**," and "**heat increment**." All of these refer to the increased heat production which follows ingestion of food. Its magnitude varies with the diet and individual and can range from 5% to 20% of the ingested calories. Usually the thermic effect is greater when the meal is larger and when the individual has a greater fat-free mass. In addition, protein in the diet exerts a much larger thermic effect than starches or fats. Measurement of the thermic effect of food is illustrated in Figure 8.6.4.

## ACTIVITY ADDS THE GREATEST INCREMENT TO METABOLISM

The single largest source of variation in energy expenditure is the level of activity. There are two main considerations when estimating the effect of physical activity: the **duration** and the **intensity**. Table 8.6.4 details the energy cost associated with physical activity, expressed in terms of milliliters of $O_2$ consumed per kilogram of body weight per minute because activity becomes energetically more costly as body size increases. It is also expressed in METS (metabolic equivalents). One MET is the average $O_2$ consumption at rest, equal to 3.5 mL of $O_2$ per kg per minute.

## THE BODY HOMEOSTATICALLY REGULATES ITS WEIGHT

Over the course of a year, most adults consume between 400 and 700 kg of food, yet their weight fluctuates at most a few kilograms. A mismatch of just 5% between food intake and energy expenditure would result in a weight gain or loss of about 5 kg per year—but most people gain or lose far less than that. **Body weight regulation is extraordinarily precise**. Major changes in body weight and composition can be forced by under- or overfeeding, or by forced exertion, but body weight returns when *ad libitum* feeding resumes.

## THE CENTRAL NERVOUS SYSTEM REGULATES FEEDING BEHAVIOR

The act of choosing what to eat, how much to eat, and when to eat it is a conscious decision that involves higher order neural processing. In the human psychosocial environment, food intake is associated with other activities. We entertain and socialize around food and attach culturally dependent status to certain foods. There are traditional breakfast foods, lunch foods, snack foods, and supper foods. Consumption is dictated by the time food is prepared rather than the time we are hungry. Food becomes much more than mere nourishment. Its presentation and social setting become as important as the food itself. On the other hand, noxious sights,

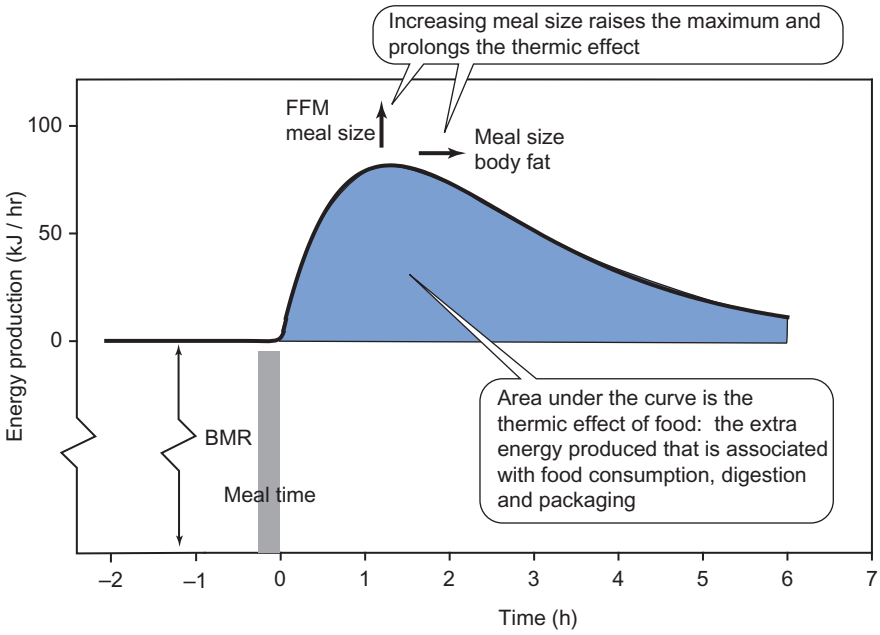


**FIGURE 8.6.4** The thermic effect of food. During rest, energy production is more or less constant. Following ingestion of a meal, heat production increases to a maximum and then tapers off back to baseline levels. The peak is affected by the size of the meal and the free fat mass (FFM). Increased meal size also prolongs the thermic effect. Increased body fat typically delays the peak of the thermic effect. The extra heat production is the area under the curve of heat production above the BMR. The curve can be fit to the equation $A + Bte^{-t/C}$ where the maximum of the curve occurs at $t = C$ at an increment of $B\ C\ e^{-1}$. For the curve shown, $B = 175.9$ kJ h$^{-2}$ and $C = 1.3$ h.

**TABLE 8.6.4** Energy Expenditure for Various Activity Levels for Men and for Women

| Exercise Intensity | Energy Expenditure | | | |
|---|---|---|---|---|
| | kcal $min^{-1}$ | L $O_2$ $min^{-1}$ | mL $O_2$ $kg^{-1}$ $min^{-1}$ | METs |
| ***Men*** | | | | |
| Light | 2.0–5.0 | 0.4–1.0 | 6–15 | 1.6–4 |
| Moderate | 5.0–7.5 | 1.0–1.5 | 15–22.5 | 4–6 |
| Heavy | 7.5–10.0 | 1.5–2.0 | 22.5–30 | 6–8 |
| Very heavy | 10.0–12.5 | 2.0–2.5 | 30–37.5 | 8–10 |
| ***Women*** | | | | |
| Light | 1.5–3.5 | 0.3–0.7 | 5.5–12.5 | 1.5–3.5 |
| Moderate | 3.5–7.5 | 0.7–1.1 | 12.5–20 | 3.5–5.5 |
| Heavy | 7.5–10.0 | 1.1–1.5 | 20–27.5 | 5.5–7.5 |
| Very heavy | 10.0–12.5 | 1.5–1.9 | 27.5–35 | 7.5–9.5 |

*Modified from W.D. McCardle, F.I. Katch, and V.L. Katch,* Exercise Physiology, *Lea and Febiger, Philadelphia, PA, 1991*

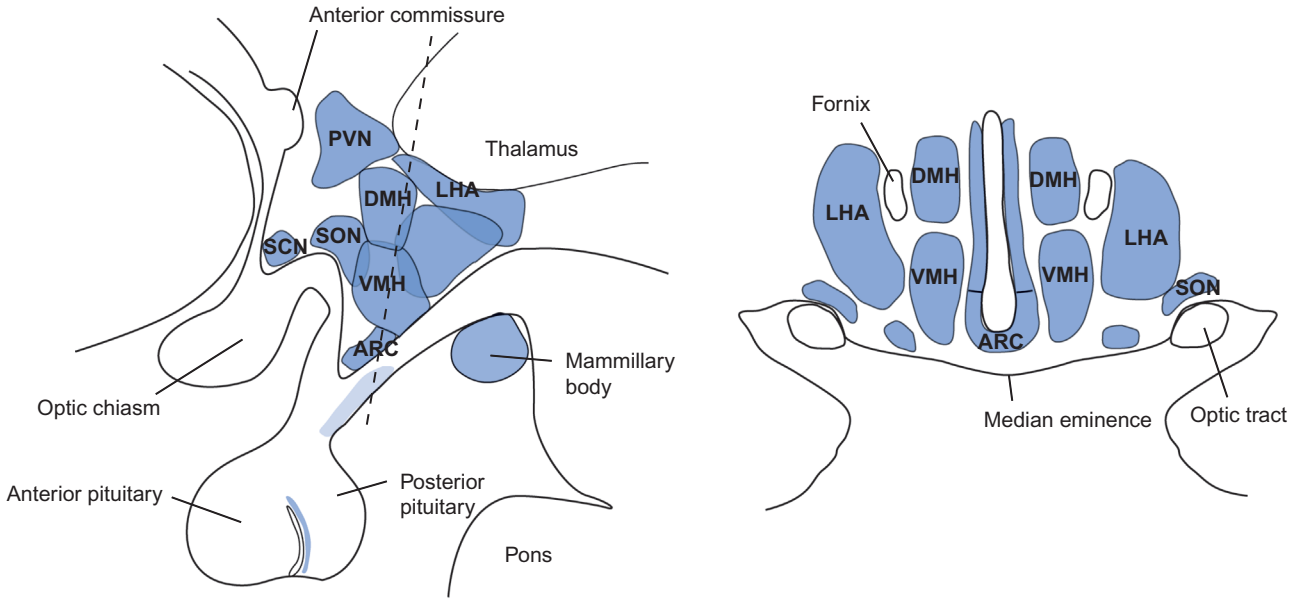


**FIGURE 8.6.5** Approximate location of hypothalamic areas involved in regulating food intake. Left, saggital section of the brain (plane perpendicular to the face). Right, coronal section (plane parallel to the face). Labeled structures include the arcuate nucleus (ARC), the paraventricular nucleus (PVN), the lateral hypothalamic area (LHA), the dorsal medial hypothalamus (DMH), and the ventral medial hypothalamus (VMH). Other structures not directly involved in food intake regulation but shown for reference include the suprachiasmatic nucleus (SCN) and the supraoptic nuclei (SON).

odors, pain, or distressful psychological events cause us to lose our appetite. Underneath all of the cultural and hedonistic aspects of consuming food are the physiological signals that instruct us how much to eat.

## EARLY STUDIES SHOWED THAT THE HYPOTHALAMUS DRIVES FEEDING BEHAVIOR

Electrolytic lesioning of the **ventromedial hypothalamus (VMH)** causes hyperphagia (excess food consumption) in rats. Conversely, electrical stimulation of this area inhibits feeding. This ventromedial hypothalamus is classically known as a **"satiety center,"** as stimulation shuts down feeding and destruction of it causes overeating and weight gain (see Figure 8.6.5).

Electrical stimulation of the **lateral hypothalamic area (LHA)** causes feeding behavior, whereas destruction by electrolytic lesioning attenuates feeding and causes weight loss. Thus this area seems to turn on feeding and so it was classically called the **"feeding center."**

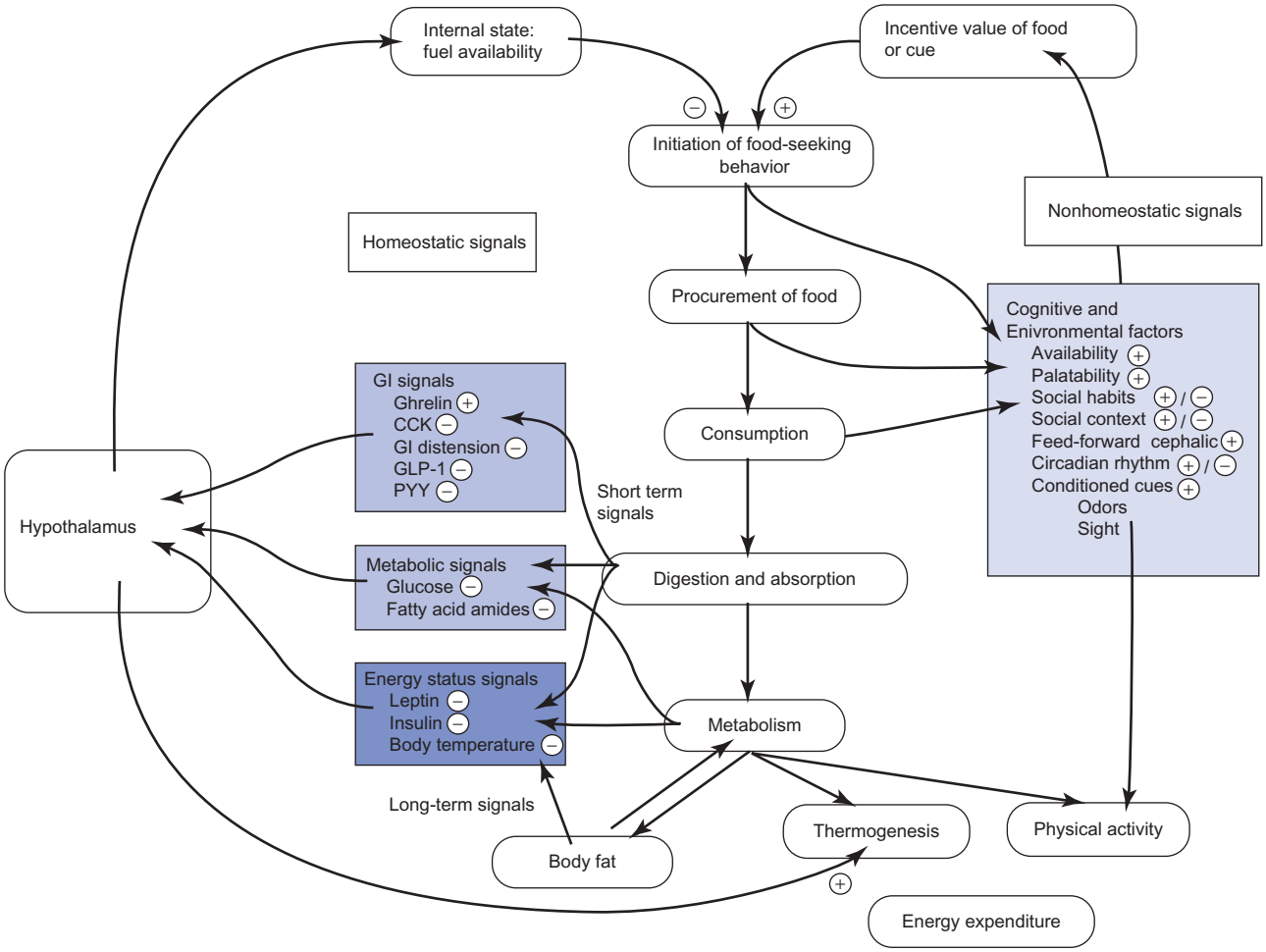


**FIGURE 8.6.6** Overall scheme for the regulation of food intake. Homeostatic signals are shown on the left of the figure; nonhomeostatic signals are on the right. Nonhomeostatic signals include all those sensory modalities that make food attractive or unattractive, including odor, sight, taste, mouth feel (all of which constitute part of palatability), and in addition the availability and social context of the food. Physical exertion is also nonhomeostatic. Homeostatic signals include short-term signals that inform the CNS about the kinds and amounts of food consumed in a meal and long-term signals that inform the CNS about the body's adiposity. Most signals from the GI tract and fuel stores shut down food intake, with the exception of ghrelin. The − and + signs refer to the effect of the signal on the indicated output when the signal increases.

## THE SIMPLISTIC EARLY VIEW IS SUPPLANTED BY A PICTURE OF MULTIPLE CENTERS AND MULTIPLE SIGNALS

Since the early studies identified "satiety center" and "feeding center," investigators have discovered a number of materials that affect food intake and have shown that multiple centers are involved. In addition to these, odors, sights, and higher order psychological events input into our subjective feeling of being hungry. Most of this work has been performed in experimental animals and so the relevance to human physiology is often not yet established. Although there is as yet no complete "wiring diagram" that describes in detail how feeding behavior is governed, much of the puzzle has been uncovered. Figure 8.6.6 shows the general scheme of how food intake and energy expenditure is regulated.

## SHORT-TERM SIGNALS LIMIT THE SIZE OF MEALS: THEY ARE SATIETY SIGNALS

Short-term signals originate from the periphery and depend on how much and what kind of food is consumed in a meal, as opposed to the body's adiposity and energy status, and limit the size of individual meals. Short-term signals that originate from the intestine or metabolism are summarized in Table 8.6.5.

All parts of the gastrointestinal tract are invested with **mechanoreceptors** that sense stretch or irritation and **chemosensors** that sense nutrients and noxious chemicals. These receptors send afferent information over the vagus nerve to the **nucleus tractus solitarius (NTS)** in the brain stem and from there to the dorsal motor nucleus of the vagus for vagovagal reflexes. The NTS also receives inputs from the sense of taste from cranial nerves VII (facial nerve) and IX (glossopharyngeal nerve).

**TABLE 8.6.5** Synopsis of Short-Term Homeostatic Mechanisms Regulating Food Intake

| Signal | Source and Secretagogues | Chemical Nature | Targets | Primary Action |
|---|---|---|---|---|
| Gut distension | Stretch receptors in stomach and small intestine | Vagal afferent nerve activity | Nucleus tractus solitarius (NTS) to parabrachial nucleus to hypothalamus | Inhibits feeding; also involved in reflexes for gut motility and secretion |
| GI chemoreceptors | Sugars, amino acids, fatty acids, and peptides in small intestine | Vagal afferent nerve activity | Nucleus tractus solitarius (NTS) to parabrachial nucleus to hypothalamus | Inhibits feeding; also involved in reflexes for gut motility and secretion |
| Cholecystokinin (CCK) | Endocrine I cells in proximal third of intestine | 83-aa chain + fragments | CCK1 receptors on vagal afferents; interacts with GI distension signals | Inhibits feeding; also increases pancreatic exocrine secretion and gallbladder contraction |
| Glucose | Digested and absorbed carbohydrates | Glucose | Glucose-responsive and glucose-sensitive neurons in hypothalamus | Inhibits feeding; increases insulin secretion and decreases glucagon secretion |
| GLP-1 | Endocrine L cells in jejunum, ileum, and colon in response to intestinal nutrients | 30-aa chain | Hypothalamus pancreatic islet cells stomach | Inhibits feeding; stimulates insulin secretion; delays gastric emptying |
| Ghrelin | Endocrine X/A cells in the stomach | 28-aa chain: acylated at ser3 | | Stimulates feeding; binds to GHS-R to stimulate GHRH release and by directly stimulating somatotrophs |
| PYY(3-36) | Endocrine cells in distal intestine in response to digestion products | 34-aa chain | Y2 receptors in the arcuate nucleus that inhibit NPY release | Inhibits feeding but probably at the next meal |

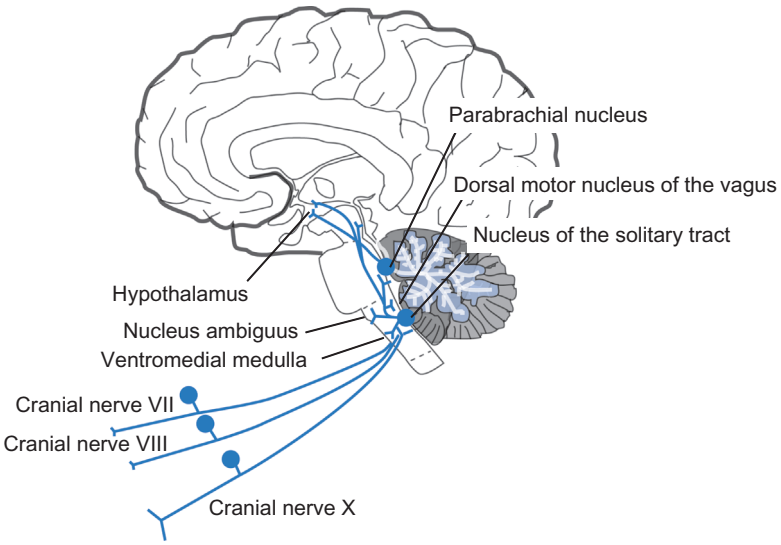


**FIGURE 8.6.7** Ascending pathways for visceral information relating to a meal. Gustatory mechanoreceptors, and chemoreceptors from the facial, glossopharyngeal, and vagus nerves all feed into the nucleus of the solitary tract (NTS) and from there ascend to the parabrachial nucleus and from there to the hypothalamus, amygdala, and cortex.

Information passes up to the hypothalamus directly and through the parabrachial nucleus. Afferent information also travels along the sympathetic nerves in the splanchnic nerves. Figure 8.6.7 shows these ascending pathways for visceral information.

As discussed in Chapter 8.2, **cholecystokinin**, or **CCK**, is secreted by endocrine I cells in the proximal intestine in response to amino acids and fat digestion products. It stimulates CCK1 receptors on afferent fibers of the vagus. These fibers may be the same as those that respond to distension, so some vagal fibers may integrate different kinds of signals related to ingestion of food. The vagal signal proceeds to the NTS which then stimulates pancreatic acinar cells to increase zymogen output. CCK is also synthesized in the hypothalamus and is used as a neurotransmitter there. The central effects of CCK remain unclear. Vagotomy only partially reduces CCK's inhibition of food intake, suggesting that both peripheral and central effects occur.

The **glucostatic hypothesis**, first proposed by Jean Mayer in 1953, holds that sensors in the brain detect hypoglycemia and then initiate subjective feelings of hunger to motivate the person to seek food. Glucose levels increase after eating a meal, and sensors detect this rise and stop eating behavior. Although this makes subjective sense, typically eating stops before

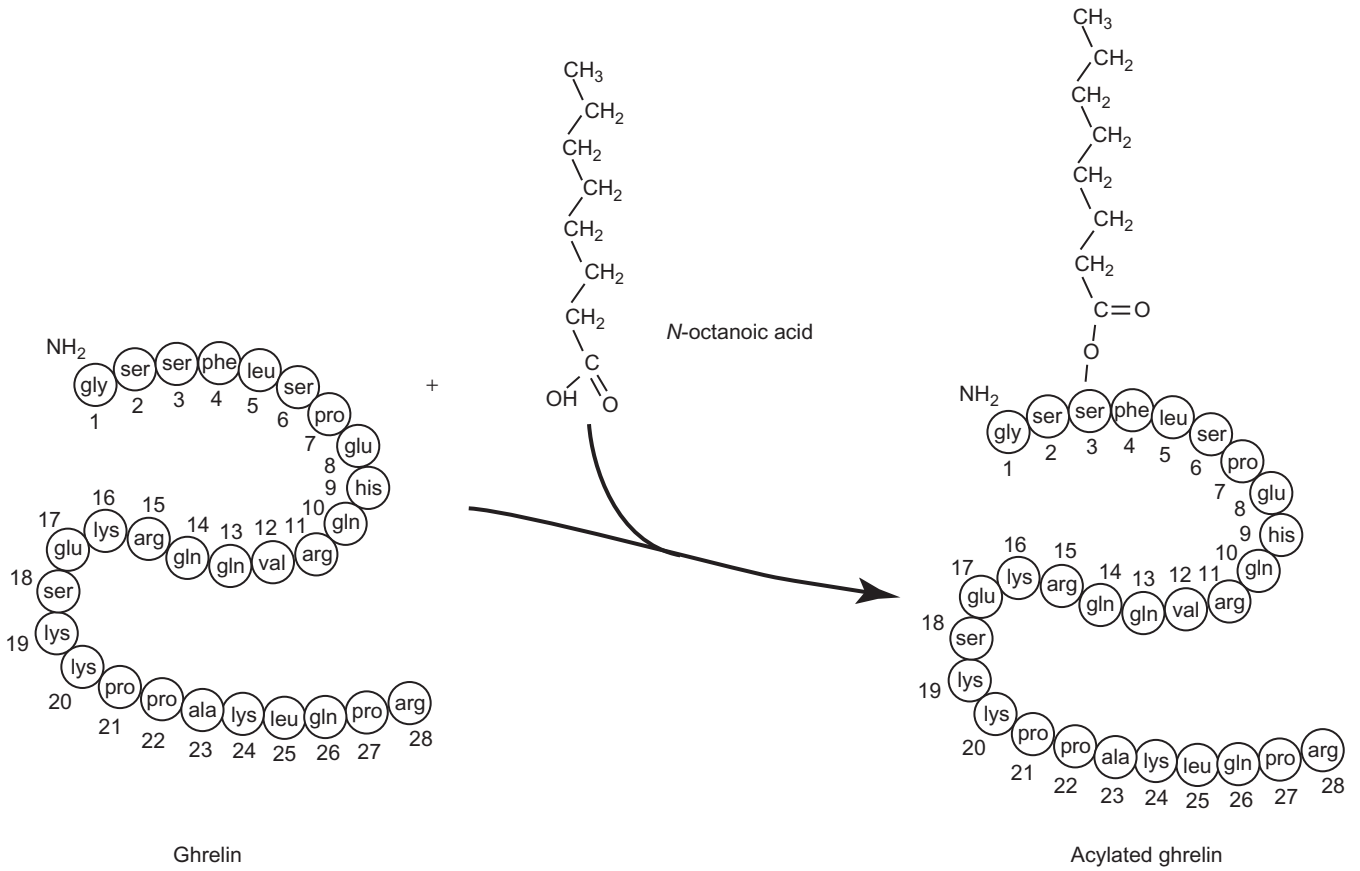


**FIGURE 8.6.8** Primary structure of ghrelin showing the addition of an octanoyl group on serine 3. Without this group, ghrelin is unable to bind to its receptors.

postprandial glucose levels rise. Nevertheless, hypoglycemia or inhibition of glucose metabolism with 2-deoxyglucose increases feeding behavior. Some neuronal cells are **glucose responsive**: they **increase their firing rate when glucose levels rise**. Others are **glucose sensitive**: they **increase their firing rate when glucose levels fall**. These neurons are alternatively described as glucose excited (GE) or glucose inhibited (GI). These glucose-sensing neurons reside in all of the hypothalamic areas important to the regulation of food intake and energy expenditure: the arcuate nucleus (ARC), dorsal medial hypothalamus (DMH), paraventricular hypothalamus (PVN), ventral medial hypothalamus (VMH), and lateral hypothalamic area (LHA). The NTS also contains glucose-sensing neurons. Glucose-responsive or glucose-excited neurons respond by depolarization by mechanisms like those in β cells of the pancreatic islets. These GE neurons also respond to other metabolites and other stimuli, suggesting that they integrate signals for feeding behavior.

**Glucagon-like peptide 1** is secreted by L-type endocrine cells that are located in the jejunum, ileum, and colon. It stimulates insulin secretion and inhibits gastric emptying. This would promote gastric distension that in turn would increase afferent vagal stimulation to inhibit feeding. The effect of GLP-1 on feeding behavior is abolished by vagotomy, but its effect on stomach emptying is not. However, GLP-1 peaks too late to effectively signal satiety to the central nervous system (CNS). GLP-1 is also synthesized in the brain, and GLP-1 receptors have been located in the supraoptic nuclei (SON), PVN, and ARC of the hypothalamus.

**Ghrelin** is a 28-aa peptide secreted primarily by endocrine cells in the stomach during fasting. Its main effects include release of growth hormone (GH) and increased feeding. Ghrelin is named because of its **g**rowth **h**ormone **rel**easing action. Ghrelin binds to **g**rowth **h**ormone **s**ecretagogue **r**eceptors (GHS-R) on cells in the ARC of the hypothalamus and on somatotrophs in the anterior pituitary. Ghrelin is unusual in that its activity requires an octanoyl group added to the hydroxyl of serine 3 (see Figure 8.6.8). Only the acylated form binds to its GHS-R, but the major part of the circulating ghrelin is unacylated. The main stimulus for ghrelin secretion is fasting, but hypoglycemia and insulin also cause ghrelin secretion. After each meal, circulating ghrelin levels fall due to inhibition of ghrelin secretion by nutrients in the stomach. Thus ghrelin may be a peripheral signal for satiety by removal of its feeding stimulation.

Ghrelin stimulates neurons in the ARC that use **neuropeptide Y** (**NPY**) and **agouti-related protein** (**AgRP**). These neurons project to neurons in the PVN, LHA, and DMH that help regulate feeding. Both NPY and AgRP

**TABLE 8.6.6** Synopsis of Long-Term Regulators of Food Intake

| Signal | Source and Secretagogues | Chemical Nature | Targets | Primary Action |
|---|---|---|---|---|
| Insulin | β Cells of pancreatic islets | 30 + 21-aa chain | Liver, muscle, fat, and brain | Regulates glucose uptake and lipolysis; inhibits feeding |
| Amylin | β Cells of pancreatic islets | 37-aa chain | Neurons in hypothalamus | Inhibits feeding |
| Leptin | Adipocytes and endocrine cells in the stomach | 146-aa chain | Neurons in the arcuate nucleus; vagal afferents | Inhibits feeding |

stimulate feeding and are called **orexigenic**. Other neurons in the ARC use α **melanocyte stimulating hormone** (αMSH) and **cocaine–amphetamine regulated transcript (CART)** as neurotransmitters. The αMSH derives from **POMC** or **proopiomelanocortin** and so the neurons are called POMC/CART neurons. These neurons ordinarily not only inhibit feeding but also regulate energy expenditure through sympathetic stimulation of adipose and muscle tissues (see Chapter 2.11, Clinical Applications: Nonshivering Thermogenesis). These POMC/CART neurons are inhibited by the NPY/AgRP neurons. Because ghrelin stimulates the orexigenic NPY/AgRP neurons, it indirectly inhibits the POMC/CART anorexigenic neurons.

**Protein YY(3-36)** is secreted from the distal intestine in response to digestion products in the lumen. In contrast to CCK, PYY(3-36) secretion occurs postprandially rather than during a meal. It exerts an **anorexigenic** effect (it inhibits food intake) through peripheral and central mechanisms. It is proposed to activate presynaptic Y2 receptors. **NPY** is released by cells in the ARC that exert potent orexigenic control. They act on Y receptors, of which there are at least six different varieties: Y1–Y6. The Y1 receptor activates feeding. Y2 receptors are on NPY cells and are autoreceptors. By activating the Y2 receptor, PYY may inhibit NPY cells in the ARC. This inhibition indirectly activates neurons that contain POMC/CART. These POMC-containing cells inhibit food intake and increase energy expenditure. Thus PYY appears to rise too late to influence meal size while it is being eaten but may reduce the size of the subsequent meal by inhibiting cells that stimulate food intake and indirectly activating cells in the ARC that inhibit food intake.

## LONG-TERM SIGNALS MAINTAIN BODY COMPOSITION: THEY ARE ADIPOSITY SIGNALS

In 1953, Kennedy formulated the **lipostatic hypothesis** for the regulation of body weight, in which fat tissue produces a signal that informs the CNS of the level of body adiposity, and the CNS accordingly activates eating or fasting to keep adipose stores constant. Hervey surgically connected the circulatory systems of two rats and then made one rat obese by destroying its satiety center, the VMH. The other rat became hypophagic and thin in response to the obesity of its partner. We now know that fat tissue secretes blood-borne substances that are detected by the CNS. In the parabiotic rats, the thin rat detected this material from its obese partner and reduced food intake, thinking that it was too fat. Thus adipose tissue makes substances that inform the CNS of the adiposity of the body. The regulatory mechanisms appear to be much better at correcting deficits of adipose tissue than excesses. The long-term signals that originate from adipose and pancreatic tissues are listed in Table 8.6.6.

Adipose tissue secretes **leptin** (from the Greek "leptos," meaning "thin") proportional to the amount of fat, so that circulating levels of leptin indicate adiposity. Leptin secretion is increased by insulin and adipocyte glucose metabolism. High fat and high fructose diets, both of which more poorly stimulate insulin secretion and blood glucose levels, are associated with lower leptin levels. This may partly explain the epidemic of obesity in Western cultures where people consume high fat diets laden with high fructose corn syrup. Leptin binds to two kinds of receptors, a "long" form, LRb, and a short form, LRa. It is transported across the blood–brain barrier by a mechanism involving LRa. After transport into the CSF, leptin binds to LRb on specific cells in the hypothalamus. This works through a JAK/STAT pathway, ending in the phosphorylation of STAT3 (see Figure 8.6.9). **Leptin suppresses appetite and increases energy expenditure.** It binds to NPY/AgRP neurons and POMC/CART neurons in the ARC. It decreases production of the orexigenic NPY and AgRP and increases production of anorexigenic αMSH and CART. In addition, leptin increases energy expenditure through activation of the sympathetic nervous system. Leptin also has receptors in the LHA and PVN.

Although insulin is secreted by β cells in the pancreatic islets of Langerhans rather than by adipocytes, the circulatory levels of insulin are also proportional to the body adiposity: fatter people secrete proportionately more insulin to a given increase in blood glucose than do leaner people. Insulin also crosses the blood–brain barrier by specific transport mechanisms, and neurons in the ARC of the hypothalamus have receptors for insulin.

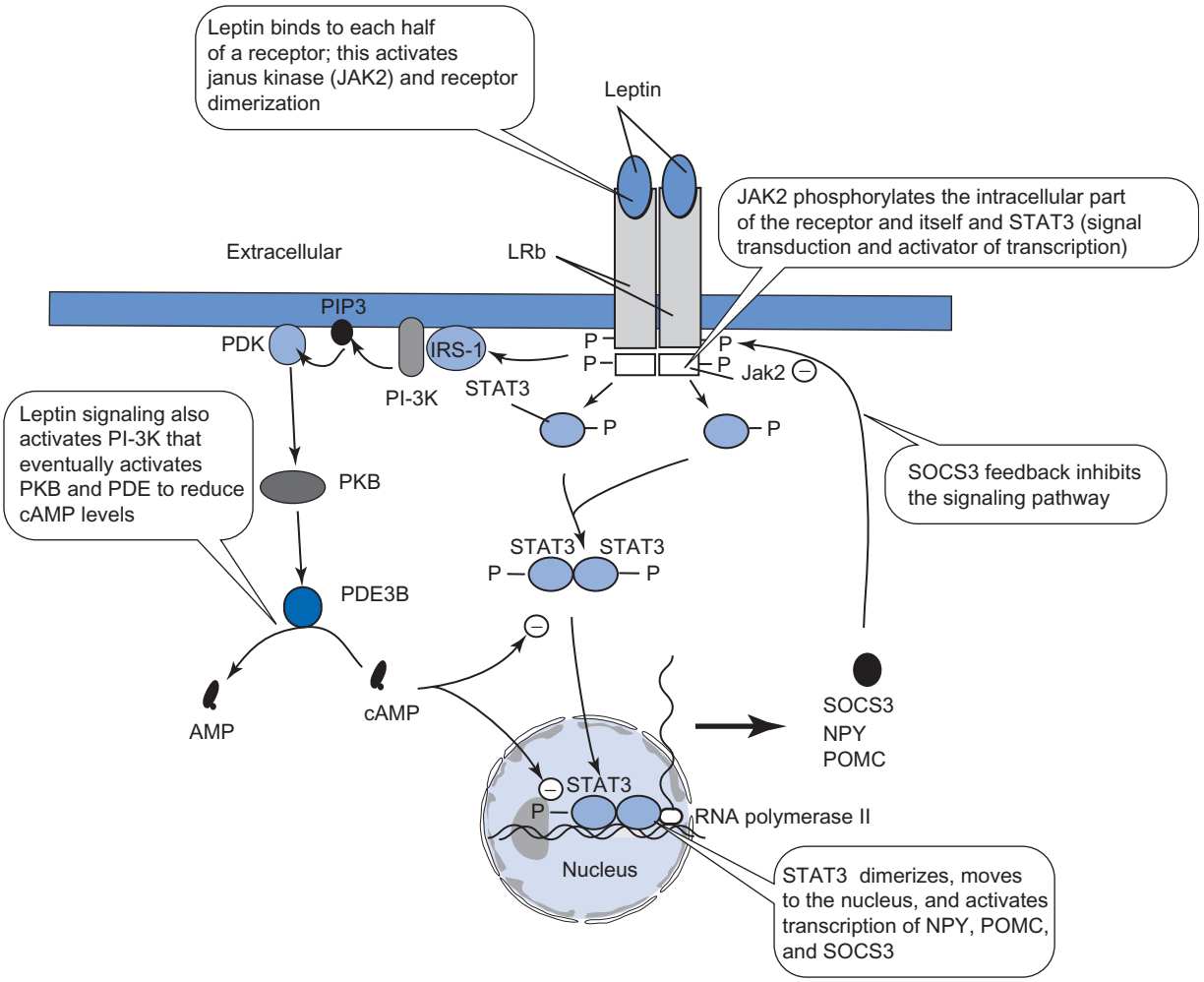


**FIGURE 8.6.9** Mechanism of action of leptin on LRb receptors. Leptin binds to each half of a receptor. This activates dimerization of the receptor and activation of its associated janus kinase (JAK2). JAK2 phosphorylates itself and the intracellular part of the receptor and other targets. One of these is STAT3, for **s**ignal **t**ransduction and **a**ctivation of **t**ranscription. The activated STAT3 dimerizes and moves to the nucleus where it enhances transcription of target genes including those coding for NPY, proopiomelanocortin (POMC), and suppressor of cytokine signaling (SOCS). Leptin also activates the phosphorylation of insulin receptor substrates (IRS-1) that bind phosphatidyl inositol 3 kinase (PI-3K) which makes PIP3 in the membrane. PIP3 in turn activates a phosphoinositide-dependent protein kinase (PDK) that in turn activates protein kinase B (PKB) which activates phosphodiesterase (PDE3B) that degrades cAMP. This removes inhibition of STAT3 transcription. SOCS3 feeds back on the receptor to inhibit its further activity.

Insulin levels rise with feeding, fall with fasting, and rise in obesity, similarly to leptin. Unlike leptin, insulin secretion is stimulated acutely in response to meals. Insulin administered into the brain suppresses food intake.

Amylin, a polypeptide containing 37 amino acids, is cosecreted with insulin in response to glucose and other nutrients. Its secretion is proportional to body adiposity. It delays gastric emptying and in experimental animals amylin reduces food intake. Like insulin, amylin is transported across the blood–brain barrier by a carrier. Low doses administered directly into the ventricles of the brain also reduce food intake, suggesting that its action lies in the brain itself rather than indirectly through inhibition of gastric emptying. Blockade of central amylin receptors leads to increased food intake. Although the data supporting amylin's role are less extensive, the evidence suggests that amylin and insulin both inform the CNS of body adiposity.

## INTEGRATED MECHANISM OF FOOD INTAKE REGULATION

The signals for food intake regulation are integrated in the hypothalamus, involving the ARC, LHA, VMH, DMH, and PVN. Neurons in these structures use a variety of neurotransmitters. Those that are orexigenic (promoting feeding behavior) include NPY/AgRP, Orexin A and B (also known as the hypocretins), and melanin concentrating hormone (MCH). Anorexigenic neurotransmitters include POMC/CART. A complete "wiring" diagram that describes the neural mechanism for regulation of food intake is hopelessly complicated for presentation here. A simplified version is shown in Figure 8.6.10.

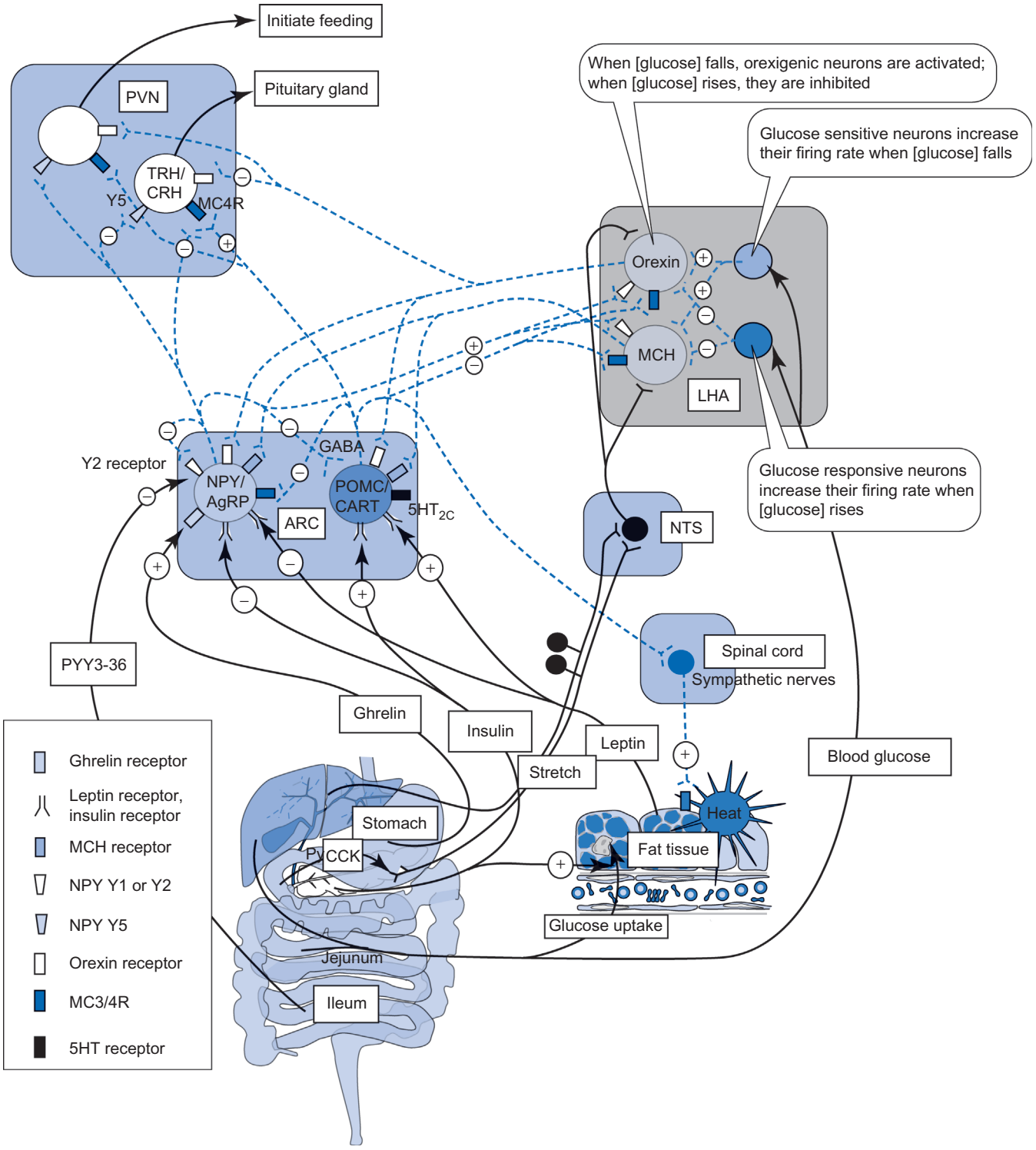


**FIGURE 8.6.10** Integrated control of food intake. Some of the connections are shown for NPY/AgRP and POMC/CART neurons in the arcuate nucleus (ARC) and for orexin and MCH neurons in the lateral hypothalamic area (LHA). Information entering the hypothalamus from the periphery is in black. Final output is also shown in black. NPY/AgRP cells in the ARC are orexigenic. They are stimulated by ghrelin, inhibited by leptin, insulin, and PYY3-36, and are sensitive to glucose (not shown). They project to cells in the PVN, LHA, and DMH (not shown) and inhibit POMC/CART cells in ARC. POMC/CART cells use αMSH as a neurotransmitter onto MC3/4R receptors. αMSH and CART are anorexigenic. These cells are stimulated by leptin and insulin and activated indirectly by PYY3-36 through its inhibition of NPY/AgRP input onto the POMC/CART cells. Orexin A- and B-containing neurons are in the LHA. They are turned on by low blood glucose and by the balance of inputs from NPY/AgRP and POMC/CART cells from the ARC. They also receive input from the NTS, the nucleus of the solitary tract.

## SUMMARY

Energy balance in humans obeys the laws of thermodynamics. The energy available from ingested food is its heat of combustion from initial foodstuff to final waste products. Glucose and fats are potentially oxidized completely, but proteins are only partially oxidized. The Atwater factors are approximations that give the available metabolic energy for fats, carbohydrates, proteins, and alcohol, and take into account digestibility and losses in urine and feces.

Energy production is nearly perfectly predicted by oxygen consumption. The amount of energy derived from fats, lipids, and carbohydrates differs markedly when expressed per gram of starting material, but it is essentially the same when expressed in terms of the oxygen consumed. Measurement of $V_{O_2}$ and $V_{CO_2}$ allows estimation of energy production. If urinary protein is also measured, the amount of fats, carbohydrates, and proteins consumed can be estimated.

The largest component of energy expenditure is the basal metabolic rate, but the greatest variable is the duration and intensity of activity. In highly active people, activity can consume more energy than maintenance. The BMR varies with age and gender and can be estimated by empirical formulas.

The hypothalamus regulates food intake by integrating a variety of signals. These include short-term satiety signals from the gastrointestinal tract and long-term adiposity signals from adipose tissue and metabolism. On top of this are the psychosocial cues including the availability, palatability, and social environment of eating.

The short-term signals nearly uniformly inhibit food intake. These include the following: GI distension; chemosensor detection of nutrients in the GI tract; CCK; blood glucose; GLP-1; and PYY3-36. All of these increase after a meal and all inhibit feeding. PYY3-36 is released from the ileum and therefore increases too late to influence food consumption at the meal. It probably influences food consumption at the next meal. Ghrelin is a 28-aa peptide produced by the stomach during fasting that increases appetite.

Blood glucose appears to regulate feeding behavior through glucose-responsive neurons that increase their firing when glucose levels rise and glucose-sensitive neurons that increase their firing rate when glucose levels fall.

The two most important long-term peripheral regulators of food intake are insulin and leptin. Adipose tissue secretes leptin in proportion to the amount of adipose tissue and insulin levels are also proportional to body adiposity. Several hypothalamic areas have receptors for both insulin and leptin. Leptin not only turns off feeding behavior but it also turns on thermogenesis through sympathetic stimulation of adipose tissue and muscle.

The central regulators of feeding behavior are classified as orexigenic (promoting feeding) and anorexigenic (inhibiting feeding). The orexigenic transmitters include NPY and agouti-related peptide (AgRP), both expressed by a population of cells in the ARC; and orexin A and B, expressed by cells in the LHA and MCH, produced by separate cells in the LHA. The main anorexigenic transmitters include αMSH, derived from POMC in cells in the ARC; and cocaine and amphetamine regulated transcript, or CART, coexpressed in POMC cells. In addition to its anorexigenic effect, POMC/CART cells activate sympathetic stimulation of the tissues, leading to increased energy expenditure.

## REVIEW QUESTIONS

1. What are the Atwater factors for protein, carbohydrate, and fats? Are they simply the results of bomb calorimetry? What is a bomb calorimeter, anyway?
2. What is indirect calorimetry? What is meant by "energy equivalent" of oxygen for proteins, fats, and carbohydrates? Why do you think the energy equivalent of oxygen is so close for all three macronutrients?
3. What is the BMR? Why is this important? What accounts for the largest part of variation in energy requirement or expenditure?
4. What part of the brain is involved in homeostatic regulation of body adiposity?
5. What short-term signals turn on feeding behavior? What short-term signals turn off feeding behavior? What is GLP-1? Where is it made? What increases its secretion? What is ghrelin? Where is it secreted? What stimulates its secretion?
6. What are glucose-responsive neurons? What are glucose-sensitive neurons? How would these influence feeding behavior?
7. What candidates are there for long-term regulation of feeding behavior? What is leptin? Where is it made? What does it do?