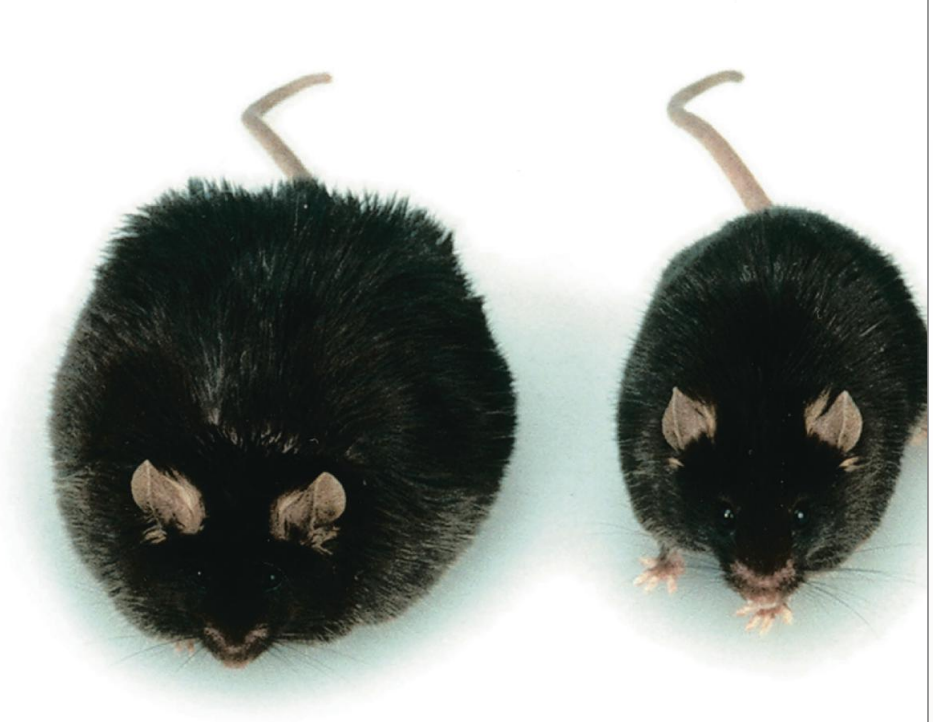
CHAPTER 16

Regulation of Organic Metabolism and Energy Balance



Genetically obese mouse and normal mouse.

Chapter 3 introduced the concepts of energy and organic metabolism at the level of the cell. This chapter deals with two topics that are concerned in one way or another with those same concepts—but for the entire body. First, this chapter describes how the metabolic pathways for carbohydrate, fat, and protein are integrated and controlled so as to provide continuous sources of energy to the various tissues and organs, even during periods of fasting. Next, the factors that determine total-body energy balance and the regulation of body temperature are described.

In Section A, you will learn how the control of metabolism is a good example of the general principle of physiology that most physiological functions are controlled by multiple regulatory systems, often working in opposition. This will be particularly evident by the opposing effects of the primary regulatory hormone insulin and the counterregulatory hormones cortisol, growth hormone, glucagon, and epinephrine on the balance of glucose and other energy sources in the blood. The control of metabolism and energy balance also illustrates the general principles of physiology that homeostasis is essential for health and survival and that physiological processes require the transfer and balance of matter and energy. In Section B, energy balance and homeostasis are again general themes. This section will also illustrate how physiological processes are dictated by the laws of chemistry and physics, particularly in relation to heat transfer between the body and the environment. ■

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16.1 Events of the Absorptive and Postabsorptive States

The regular availability of food is a very recent event in the history of humankind and, indeed, is still not universal. It is not surprising, therefore, that mechanisms have evolved for survival during alternating periods of food availability and fasting. The two functional states the body undergoes in providing energy for cellular activities are the **absorptive state,** during which ingested nutrients enter the blood from the gastrointestinal tract, and the **postabsorptive state,** during which the gastrointestinal tract is empty of nutrients and the body's own stores must supply energy. Because an average meal requires approximately 4 h for complete absorption, our usual three-meal-a-day pattern places us in the postabsorptive state during the late morning, again in the late afternoon, and during most of the night. We will refer to more than 24 h without eating as fasting.

During the absorptive state, some of the ingested nutrients provide the immediate energy requirements of the body and the remainder is added to the body's energy stores to be called upon during the next postabsorptive state. Total-body energy stores are adequate for the average person to withstand a fast of many weeks, provided water is available.

Absorptive State

The events of the absorptive state are summarized in **Figure 16.1**. A typical meal contains all three of the major energy-supplying food groups—carbohydrates, fats, and proteins—with carbohydrates constituting most of a typical meal's energy content (calories). Recall from Chapter 15 that carbohydrates and proteins are absorbed primarily as monosaccharides and amino acids, respectively, into the blood leaving the gastrointestinal tract. In contrast to monosaccharides and amino acids, fat is absorbed into the lymph in chylomicrons, which are too large to enter capillaries. The lymph then drains into the systemic venous system.

Absorbed Carbohydrate Some of the carbohydrates absorbed from the gastrointestinal tract are galactose and fructose. Because these sugars are either converted to glucose by the liver or enter essentially the same metabolic pathways as glucose, we will for simplicity refer to absorbed carbohydrates as glucose.

Glucose is the body's major energy source during the absorptive state. Much of the absorbed glucose enters cells and is catabolized to carbon dioxide and water, in the process releasing energy that is used for ATP formation (as described in Chapter 3). Skeletal muscle makes up the majority of body mass, so it is the major consumer of glucose, even at rest. Skeletal muscle not only

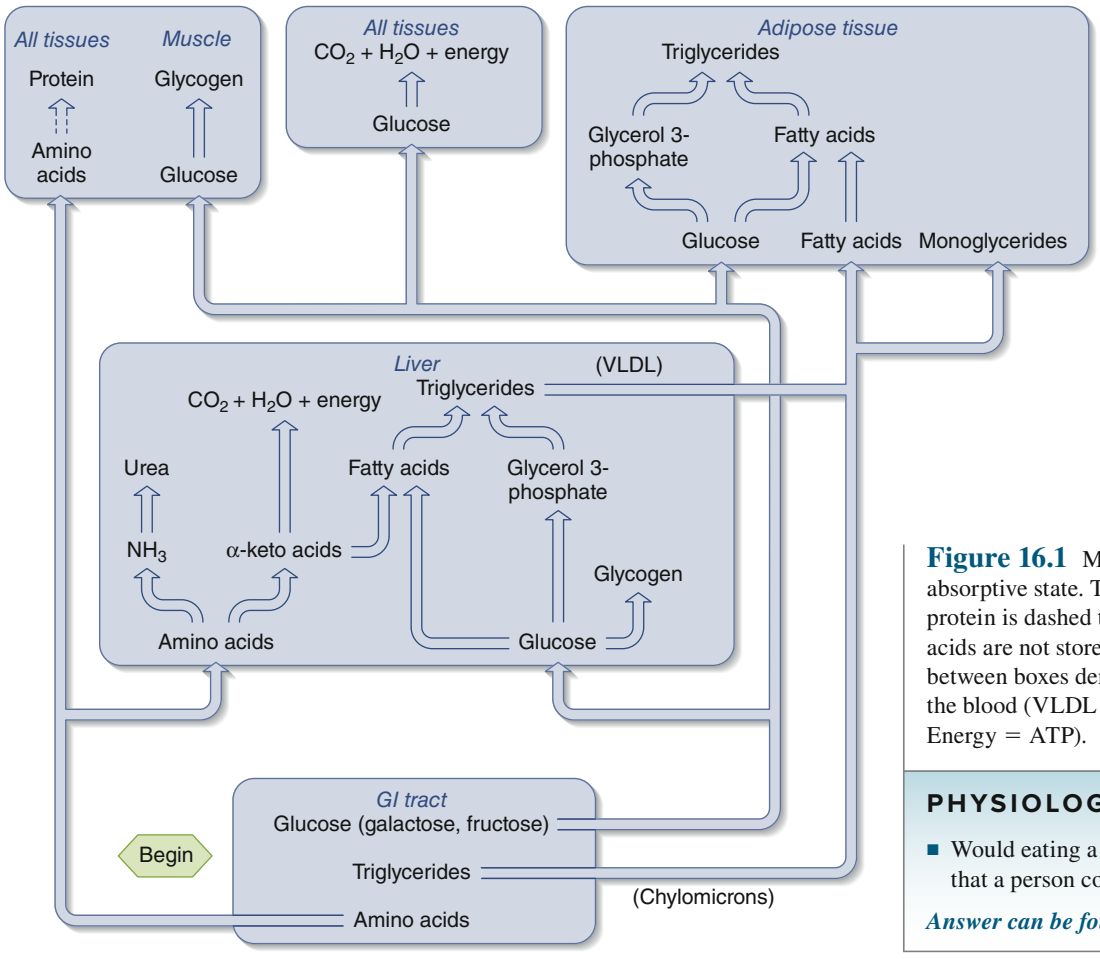


Figure 16.1 Major metabolic pathways of the absorptive state. The arrow from amino acids to protein is dashed to denote the fact that excess amino acids are not stored as protein (see text). All arrows between boxes denote transport of the substance via the blood (VLDL = very-low-density lipoproteins; Energy = ATP).

PHYSIOLOGICAL INQUIRY

- Would eating a diet that is low in fat content ensure that a person could not gain fat mass?

Answer can be found at end of chapter.

catabolizes glucose during the absorptive state but also converts some of the glucose to the polysaccharide glycogen, which is then stored in muscle cells for future use.

Adipose-tissue cells (adipocytes) also catabolize glucose for energy, but the most important fate of glucose in adipocytes during the absorptive state is its transformation to fat (triglycerides). Glucose is the precursor of both glycerol 3-phosphate and fatty acids, and these molecules are then linked together to form triglycerides, which are stored in the cell.

Another large fraction of the absorbed glucose enters liver cells. This is a very important point: During the absorptive state, there is net *uptake* of glucose by the liver. It is either stored as glycogen, as in skeletal muscle, or transformed to glycerol 3-phosphate and fatty acids, which are then used to synthesize triglycerides, as in adipose tissue. Most of the fat synthesized from glucose in the liver is packaged along with specific proteins into molecular aggregates of lipids and proteins that belong to the general class of particles known as **lipoproteins.** These aggregates are secreted by the liver cells and enter the blood. In this case, they are called **very-low-density lipoproteins** (**VLDLs**) because they contain much more fat than protein and fat is less dense than protein. The synthesis of VLDLs by liver cells occurs by processes similar to those for the synthesis of chylomicrons by intestinal mucosal cells, as Chapter 15 described.

Because of their large size, VLDLs in the blood do not readily penetrate capillary walls. Instead, their triglycerides are hydrolyzed mainly to monoglycerides (glycerol linked to one fatty acid) and fatty acids by the enzyme **lipoprotein lipase.** This enzyme is located on the blood-facing surface of capillary endothelial cells, especially those in adipose tissue. In adipose-tissue capillaries, the fatty acids generated by the action of lipoprotein lipase diffuse from the capillaries into the adipocytes. There, they combine with glycerol 3-phosphate, supplied by glucose metabolites, to form triglycerides once again. As a result, most of the fatty acids in the VLDL triglycerides originally synthesized from glucose by the *liver* end up being stored in triglyceride in *adipose tissue.* Some of the monoglycerides formed in the blood by the action of lipoprotein lipase in adipose-tissue capillaries are also taken up by adipocytes, where enzymes can reattach fatty acids to the two available carbon atoms of the monoglyceride and thereby form a triglyceride. In addition, some of the monoglycerides travel via the blood to the liver, where they are metabolized.

To summarize, the major fates of glucose during the absorptive phase are (1) utilization for energy, (2) storage as glycogen in liver and skeletal muscle, and (3) storage as fat in adipose tissue.

Absorbed Lipids As described in Chapter 15, many of the absorbed lipids are packaged into chylomicrons that enter the lymph and, from there, the circulation. The processing of the triglycerides in chylomicrons in plasma is similar to that just described for VLDLs produced by the liver. The fatty acids of plasma chylomicrons are released, mainly within adipose-tissue capillaries, by the action of endothelial lipoprotein lipase. The released fatty acids then diffuse into adipocytes and combine with glycerol 3-phosphate, synthesized in the adipocytes from glucose metabolites, to form triglycerides.

The importance of glucose for triglyceride synthesis in adipocytes cannot be overemphasized. Adipocytes do not have the enzyme required for phosphorylation of glycerol, so glycerol 3-phosphate can be formed in these cells only from glucose metabolites (refer back to Figure 3.41 to see how these metabolites are produced) and not from glycerol or any other fat metabolites.

In contrast to glycerol 3-phosphate, there are three major sources of the fatty acids found in adipose-tissue triglyceride: (1) glucose that enters adipose tissue and is broken down to provide building blocks for the synthesis of fatty acids; (2) glucose that is used in the liver to form VLDL triglycerides, which are transported in the blood and taken up by the adipose tissue; and (3) ingested triglycerides transported in the blood in chylomicrons and taken up by adipose tissue. As we have seen, sources (2) and (3) require the action of lipoprotein lipase to release the fatty acids from the circulating triglycerides.

This description has emphasized the *storage* of ingested fat. For simplicity, Figure 16.1 does not include the fraction of the ingested fat that is not stored but is oxidized during the absorptive state by various organs to provide energy. The relative amounts of carbohydrate and fat used for energy during the absorptive state depend largely on the content of the meal.

One very important absorbed lipid found in chylomicrons—**cholesterol**—does not serve as a metabolic energy source but instead is a component of plasma membranes and a precursor for bile salts and steroid hormones. Despite its importance, however, cholesterol in excess can also contribute to disease. Specifically, high plasma concentrations of cholesterol enhance the development of ***atherosclerosis,*** the arterial thickening that may lead to heart attacks, strokes, and other forms of cardiovascular damage (Chapter 12).

The control of cholesterol balance in the body provides an opportunity to illustrate the importance of the general principle of physiology that homeostasis is essential for health and survival. **Figure 16.2** illustrates a schema for cholesterol balance. The two sources of cholesterol are dietary cholesterol and cholesterol synthesized within the body. Dietary cholesterol comes from animal sources, egg yolk being by far the richest in this lipid (a single large egg contains about 185 mg of cholesterol). Not all ingested cholesterol is absorbed into the blood, however; some simply passes through the length of the gastrointestinal tract and is excreted in the feces.

In addition to using ingested cholesterol, almost all cells can synthesize some of the cholesterol required for their own plasma membranes, but most cannot do so in adequate amounts and depend upon receiving cholesterol from the blood. This is also true of the endocrine cells that produce steroid hormones from cholesterol. Consequently, most cells *remove* cholesterol from the blood. In contrast, the liver and small intestine can produce large amounts of cholesterol, most of which *enters* the blood for use elsewhere.

Now we look at the other side of cholesterol balance—the pathways, all involving the liver, for net cholesterol loss from the body. First, some plasma cholesterol is taken up by liver cells and secreted into the bile, which carries it to the gallbladder and from there to the lumen of the small intestine. Here, it is treated much like ingested cholesterol, some being absorbed back into the blood and the remainder excreted in the feces. Second, much of the cholesterol taken up by the liver cells is

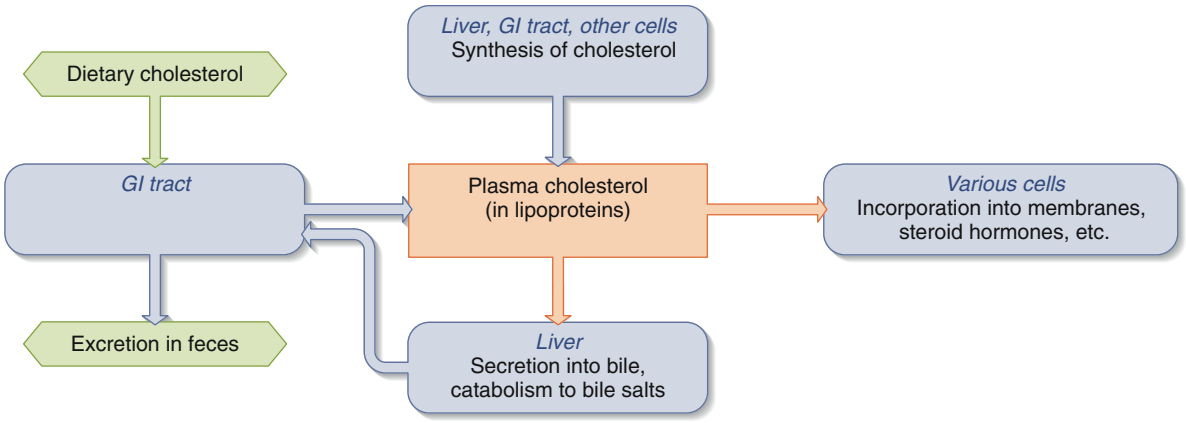


Figure 16.2 Cholesterol balance. Most of the cholesterol that is converted to bile salts, stored in the gallbladder, and secreted into the intestine gets recycled back to the liver. Changes in dietary cholesterol can modify plasma cholesterol concentration, but not usually dramatically. Cholesterol synthesis by the liver is up-regulated when dietary cholesterol is decreased, and vice versa.

metabolized into bile salts (Chapter 15). After their production by the liver, these bile salts, like secreted cholesterol, eventually flow through the bile duct into the small intestine. (As described in Chapter 15, many of these bile salts are then reclaimed by absorption back into the blood across the epithelium of the distal small intestine.)

The liver is clearly the major organ that controls cholesterol homeostasis, for the liver can add newly synthesized cholesterol to the blood and it can remove cholesterol from the blood, secreting it into the bile or metabolizing it to bile salts. The homeostatic control mechanisms that keep plasma cholesterol concentrations within a normal range operate on all of these hepatic processes, but the single most important response involves cholesterol synthesis. The liver's synthesis of cholesterol is inhibited whenever dietary—and, therefore, plasma—cholesterol is increased. This is because cholesterol inhibits the enzyme HMG-CoA reductase, which is critical for cholesterol synthesis by the liver.

Thus, as soon as the plasma cholesterol concentration increases because of cholesterol ingestion, hepatic synthesis of cholesterol is inhibited and the plasma concentration of cholesterol remains close to its original value. Conversely, when dietary cholesterol is reduced and plasma cholesterol decreases, hepatic synthesis is stimulated (released from inhibition). This increased synthesis opposes any further decrease in plasma cholesterol. The sensitivity of this negative feedback control of cholesterol synthesis differs greatly from person to person, but it is the major reason why, for most people, it is difficult to decrease plasma cholesterol concentration very much by altering only dietary cholesterol.

A variety of drugs now in common use are also capable of decreasing plasma cholesterol by influencing one or more of the metabolic pathways for cholesterol—for example, inhibiting HMG-CoA reductase—or by interfering with intestinal absorption of bile salts.

The story is more complicated than this, however, because not all plasma cholesterol has the same function or significance for disease. Like most other lipids, cholesterol circulates in the plasma as part of various lipoprotein complexes. These include chylomicrons, VLDLs, **low-density lipoproteins** (**LDLs**), and **high-density lipoproteins** (**HDLs**), each distinguished by their relative amounts of fat and protein. LDLs are the main cholesterol carriers, and they *deliver* cholesterol to cells throughout the body. LDLs bind to plasma membrane receptors specific for a protein component of the LDLs and are then taken up by the cells by endocytosis. In contrast to LDLs, HDLs *remove* excess cholesterol from blood and tissue, including the cholesterol-loaded cells of atherosclerotic plaques. They then deliver this cholesterol to the liver, which secretes it into the bile or converts it to bile salts. Along with LDLs, HDLs also deliver cholesterol to steroid-producing endocrine cells. Uptake of the HDLs by the liver and these endocrine cells is facilitated by the presence in their plasma membranes of large numbers of receptors specific for HDLs, which bind to the receptors and then are taken into the cells.

LDL cholesterol is often designated "bad" cholesterol because a high plasma concentration can be associated with increased deposition of cholesterol in arterial walls and a higher incidence of heart attacks. (The designation "bad" should not obscure the fact that LDL cholesterol is essential for supplying cells with the cholesterol they require to synthesize cell membranes and, in the case of the gonads and adrenal glands, steroid hormones.) Using the same criteria, HDL cholesterol has been designated "good" cholesterol.

The best single indicator of the likelihood of developing atherosclerotic disease is not necessarily total plasma cholesterol concentration but, rather, the ratio of plasma LDL cholesterol to plasma HDL cholesterol—the lower the ratio, the lower the risk. Cigarette smoking, a known risk factor for heart attacks, decreases plasma HDL, whereas weight reduction (in overweight persons) and regular exercise usually increase it. Estrogen not only decreases LDL but increases HDL, which explains, in part, why the incidence of coronary artery disease in premenopausal women is lower than in men. After menopause, the cholesterol values and coronary artery disease rates in women not on estrogen-replacement therapy become similar to those in men.

A variety of disorders of cholesterol metabolism have been identified. In ***familial hypercholesterolemia,*** for example, LDL

receptors are decreased in number or are nonfunctional. Consequently, LDL accumulates in the blood to very high concentrations. If untreated, this disease may result in atherosclerosis and heart disease at unusually young ages.

Finally, it is becoming clear that LDLs exist in at least two different forms ("a" and "b") distinguished by their size. The smaller of these forms, LDL-b, appears to be most closely associated with human disease and is now the focus of considerable research.

Absorbed Amino Acids Some amino acids are absorbed into liver cells and used to synthesize a variety of proteins, including liver enzymes and plasma proteins, or they are converted to carbohydrate-like intermediates known as **α-keto acids** by removal of the amino group. This process is called deamination. The amino groups are used to synthesize urea in the liver, which enters the blood and is excreted by the kidneys. The α-keto acids can enter the Krebs (tricarboxylic acid) cycle (see Chapter 3, Figure 3.44) and be catabolized to provide energy for the liver cells. They can also be used to synthesize fatty acids, thereby participating in fat synthesis by the liver.

Most ingested amino acids are not taken up by liver cells but instead enter other cells (see Figure 16.1), where they are used to synthesize proteins. All cells require a constant supply of amino acids for protein synthesis and participate in protein metabolism.

Protein synthesis is represented by a dashed arrow in Figure 16.1 to call attention to an important fact: There is a net synthesis of protein during the absorptive state, but this just replaces the proteins catabolized during the postabsorptive state. In other words, excess amino acids are not stored as protein in the sense that glucose is stored as glycogen or that both glucose and fat are stored as triglycerides. Rather, ingested amino acids in excess of those required to maintain a stable rate of protein turnover are converted to carbohydrate or triglycerides. Therefore, eating large amounts of protein does not in itself cause increases in total-body protein. Increased daily consumption of protein does, however, provide the amino acids required to support the high rates of protein synthesis occurring in growing children or in adults who increase muscle mass by engaging in weight-bearing exercises.

Table 16.1 summarizes nutrient metabolism during the absorptive state.

TABLE 16.1 Summary of Nutrient Metabolism During the Absorptive State

Energy is provided primarily by absorbed carbohydrate in a typical meal.
There is net uptake of glucose by the liver.
Some carbohydrate is stored as glycogen in liver and muscle, but most carbohydrates and fats in excess of that used for energy are stored as fat in adipose tissue.
There is some synthesis of body proteins from absorbed amino acids. The remaining amino acids in dietary protein are used for energy or converted to fat.

Postabsorptive State

As the absorptive state ends, net synthesis of glycogen, triglycerides, and protein ceases and net catabolism of all these substances begins. The events of the postabsorptive state are summarized in **Figure 16.3**. The overall significance of these events can be understood in terms of the essential problem during the postabsorptive state: No glucose is being absorbed from the gastrointestinal tract, yet the plasma glucose concentration must be homeostatically maintained because the central nervous system normally utilizes only glucose for energy. If the plasma glucose concentration decreases too much, alterations of neural activity occur, ranging from subtle impairment of mental function to seizures, coma, and even death.

Like cholesterol, the control of glucose balance is another classic example of the general principle of physiology that homeostasis is essential for health and survival. The events that maintain plasma glucose concentration fall into two categories: (1) reactions that provide sources of blood glucose; and (2) cellular utilization of fat for energy, thereby "sparing" glucose.

Sources of Blood Glucose The sources of blood glucose during the postabsorptive state are as follows (see Figure 16.3):

1. **Glycogenolysis,** the hydrolysis of glycogen stores to monomers of glucose 6-phosphate, occurs in the liver. Glucose 6-phosphate is then enzymatically converted to glucose, which then enters the blood. Hepatic glycogenolysis begins within seconds of an appropriate stimulus, such as sympathetic nervous system activation. As a result, it is the first line of defense in maintaining the plasma glucose concentration within a homeostatic range. The amount of glucose available from this source, however, can supply the body's requirements for only several hours before hepatic glycogen is nearly depleted.

   Glycogenolysis also occurs in skeletal muscle, which contains approximately the same amount of glycogen as the liver. Unlike the liver, however, muscle cells lack the enzyme necessary to form glucose from the glucose 6-phosphate formed during glycogenolysis; therefore, muscle glycogen is not a source of blood glucose. Instead, the glucose 6-phosphate undergoes glycolysis within muscle cells to yield ATP, pyruvate, and lactate. The ATP and pyruvate are used directly by the muscle cell. Some of the lactate, however, enters the blood, circulates to the liver, and is used to synthesize glucose, which can then leave the liver cells to enter the blood. Thus, muscle glycogen contributes to the blood glucose indirectly via the liver's processing of lactate.
2. The catabolism of triglycerides in adipose tissue yields glycerol and fatty acids, a process termed **lipolysis.** The glycerol and fatty acids then enter the blood by diffusion. The glycerol reaching the liver is used to synthesize glucose. Thus, an important source of glucose during the postabsorptive state is the glycerol released when adipose-tissue triglyceride is broken down.
3. A few hours into the postabsorptive state, protein becomes another source of blood glucose. Large quantities of protein in muscle and other tissues can be catabolized without serious cellular malfunction. There are, of course, limits to

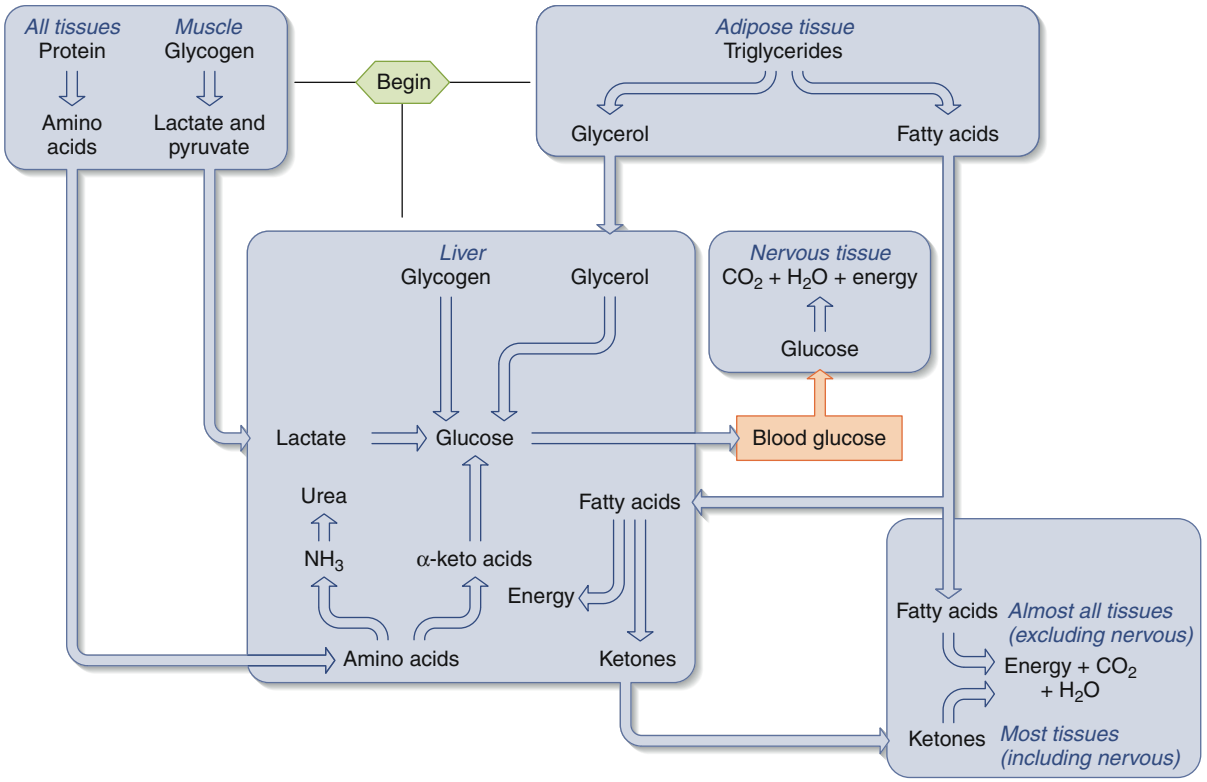


Figure 16.3 Major metabolic pathways of the postabsorptive state. The central focus is regulation of the blood glucose concentration. All arrows between boxes denote transport of the substance via the blood.

PHYSIOLOGICAL INQUIRY

- A general principle of physiology is that physiological processes require the transfer and balance of matter and energy. How is this principle apparent in the metabolic events of the postabsorptive state?

Answer can be found at end of chapter.

this process, and continued protein loss during a prolonged fast ultimately means disruption of cell function, sickness, and death. Before this point is reached, however, protein breakdown can supply large quantities of amino acids. These amino acids enter the blood and are taken up by the liver, where some can be metabolized via the α-keto acid pathway to glucose. This glucose is then released into the blood.

Synthesis of glucose from such precursors as amino acids and glycerol is known as **gluconeogenesis**—that is, "creation of new glucose." During a 24 h fast, gluconeogenesis provides approximately 180 g of glucose. Although historically this process was considered to be almost entirely carried out by the liver with a small contribution by the kidneys, recent evidence strongly suggests that the kidneys contribute much more to gluconeogenesis than previously believed.

Glucose Sparing (Fat Utilization)

The approximately 180 g of glucose per day produced by gluconeogenesis in the liver (and kidneys) during fasting supplies about 720 kcal of energy. As described later in this chapter, typical total energy expenditure for an average adult is 1500 to 3000 kcal/day. Therefore, gluconeogenesis cannot supply all the energy demands of the body during fasting. An adjustment must therefore take place during the transition from the absorptive to the postabsorptive state. Most organs and tissues, other than those of the nervous system, significantly decrease their glucose catabolism and increase their fat utilization, the latter becoming the major energy source. This metabolic adjustment, known as **glucose sparing,** "spares" the glucose produced by the liver for use by the nervous system.

The essential step in this adjustment is lipolysis, the catabolism of adipose-tissue triglyceride, which liberates glycerol and fatty acids into the blood. We described lipolysis earlier in terms of its importance in providing glycerol to the liver as a substrate for the synthesis of glucose. Now, we focus on the liberated fatty acids, which circulate bound to the plasma protein albumin, which acts as a carrier for these hydrophobic molecules. (Despite this binding to protein, they are known as free fatty acids [FFAs] because they are "free" of their attachment to glycerol.) The circulating FFAs are taken up and metabolized by almost all tissues, *excluding the nervous system.* They provide energy in two ways (see Chapter 3 for details): (1) They first undergo beta oxidation to yield hydrogen atoms (that go on to participate in oxidative phosphorylation) and acetyl CoA, and (2) the acetyl CoA enters the Krebs cycle and is catabolized to carbon dioxide and water.

In the special case of the liver, however, most of the acetyl CoA it forms from fatty acids during the postabsorptive state does not enter the Krebs cycle but is processed into three compounds collectively called **ketones,** or ketone bodies. (*Note:* Ketones are not the same as α-keto acids, which, as we have seen, are metabolites of amino acids.) Ketones are released into the blood and provide an important energy source during prolonged fasting for many tissues, *including* those of the nervous system, capable of oxidizing them via the Krebs cycle. One of the ketones is acetone, some of which is exhaled and accounts in part for the distinctive breath odor of individuals undergoing prolonged fasting.

The net result of fatty acid and ketone utilization during fasting is the provision of energy for the body while at the same time sparing glucose for the brain and nervous system. Moreover, as just emphasized, the brain can use ketones for an energy source, and it does so increasingly as ketones build up in the blood during the first few days of a fast. The survival value of this phenomenon is significant; when the brain decreases its glucose requirement by utilizing ketones, much less protein breakdown is required to supply amino acids for gluconeogenesis. Consequently, the ability to withstand a long fast without serious tissue damage is enhanced.

Table 16.2 summarizes the events of the postabsorptive state. The combined effects of glycogenolysis, gluconeogenesis, and the switch to fat utilization are so efficient that, after several days of complete fasting, the plasma glucose concentration is decreased by only a few percentage points. After 1 month, it is decreased by only 25% (although in very thin persons, this happens much sooner).

16.2 Endocrine and Neural Control of the Absorptive and Postabsorptive States

We now turn to the endocrine and neural factors that control and integrate these metabolic pathways. We will focus primarily on the following questions, summarized in **Figure 16.4**: (1) What controls net anabolism of protein, glycogen, and triglyceride in the absorptive phase, and net catabolism in the postabsorptive state? (2) What induces the cells to utilize primarily glucose for energy during the absorptive state but fat during the postabsorptive state? (3) What stimulates net glucose uptake by the liver during the absorptive state but gluconeogenesis and glucose release during the postabsorptive state?

The most important controls of these transitions from feasting to fasting, and vice versa, are two pancreatic hormones—**insulin** and **glucagon.** Also having a function are the hormones epinephrine and cortisol from the adrenal glands, growth hormone from the anterior pituitary gland, and the sympathetic nerves to the liver and adipose tissue.

Insulin and glucagon are polypeptide hormones secreted by the **islets of Langerhans** (or, simply, pancreatic islets), clusters of endocrine cells in the pancreas. There are several distinct types of islet cells, each of which secretes a different hormone. The beta cells (or B cells) are the source of insulin, and the alpha cells (or A cells) are the source of glucagon. There are other molecules secreted by still other islet cells, but the functions of these other molecules in humans are less well established.

TABLE 16.2 Summary of Nutrient Metabolism During the Postabsorptive State

Glycogen, fat, and protein syntheses are curtailed, and net breakdown occurs.
Glucose is formed in the liver both from the glycogen stored there and by gluconeogenesis from blood-borne lactate, pyruvate, glycerol, and amino acids. The kidneys also perform gluconeogenesis during a prolonged fast.
The glucose produced in the liver (and kidneys) is released into the blood, but its utilization for energy is greatly decreased in muscle and other nonneural tissues.
Lipolysis releases adipose-tissue fatty acids into the blood, and the oxidation of these fatty acids by most cells and of ketones produced from them by the liver provides most of the body's energy supply.
The brain continues to use glucose but also starts using ketones as they build up in the blood.

Insulin

Insulin is the most important controller of organic metabolism. Its secretion—and, therefore, its plasma concentration—is increased during the absorptive state and decreased during the postabsorptive state.

The metabolic effects of insulin are exerted mainly on muscle cells (both cardiac and skeletal), adipocytes, and hepatocytes. **Figure 16.5** summarizes the most important responses of these target cells. Compare the top portion of this figure to Figure 16.1 and to the left panel of Figure 16.4, and you will see that the responses to an increase in insulin are the same as the events of the absorptive-state pattern. Conversely, the effects of a decrease in plasma insulin are the same as the events of the postabsorptive pattern in Figure 16.3 and the right panel of Figure 16.4. The reason for these correspondences is that an increased plasma concentration of insulin is the major cause of the absorptive-state events, and a decreased plasma concentration of insulin is the major cause of the postabsorptive events.

Like all polypeptide hormones, insulin induces its effects by binding to specific receptors on the plasma membranes of its target cells. This binding triggers signal transduction pathways that influence the plasma membrane transport proteins and intracellular enzymes of the target cell. For example, in skeletal muscle cells and adipocytes, an increased insulin concentration stimulates cytoplasmic vesicles that contain a particular type of glucose transporter (GLUT-4) in their membranes to fuse with the plasma membrane (**Figure 16.6**). The increased number of plasma membrane glucose transporters resulting from this fusion results in a greater rate of glucose diffusion from the extracellular fluid into the cells by facilitated diffusion. This regulated movement of a transmembrane transporter illustrates the general principle of physiology that controlled exchange of materials (in this case, glucose) occurs between compartments and across cellular membranes.

Recall from Chapter 4 that glucose enters most body cells by facilitated diffusion. Multiple subtypes of glucose transporters mediate this process, however, and the subtype GLUT-4, which is regulated by insulin, is found mainly in skeletal muscle cells

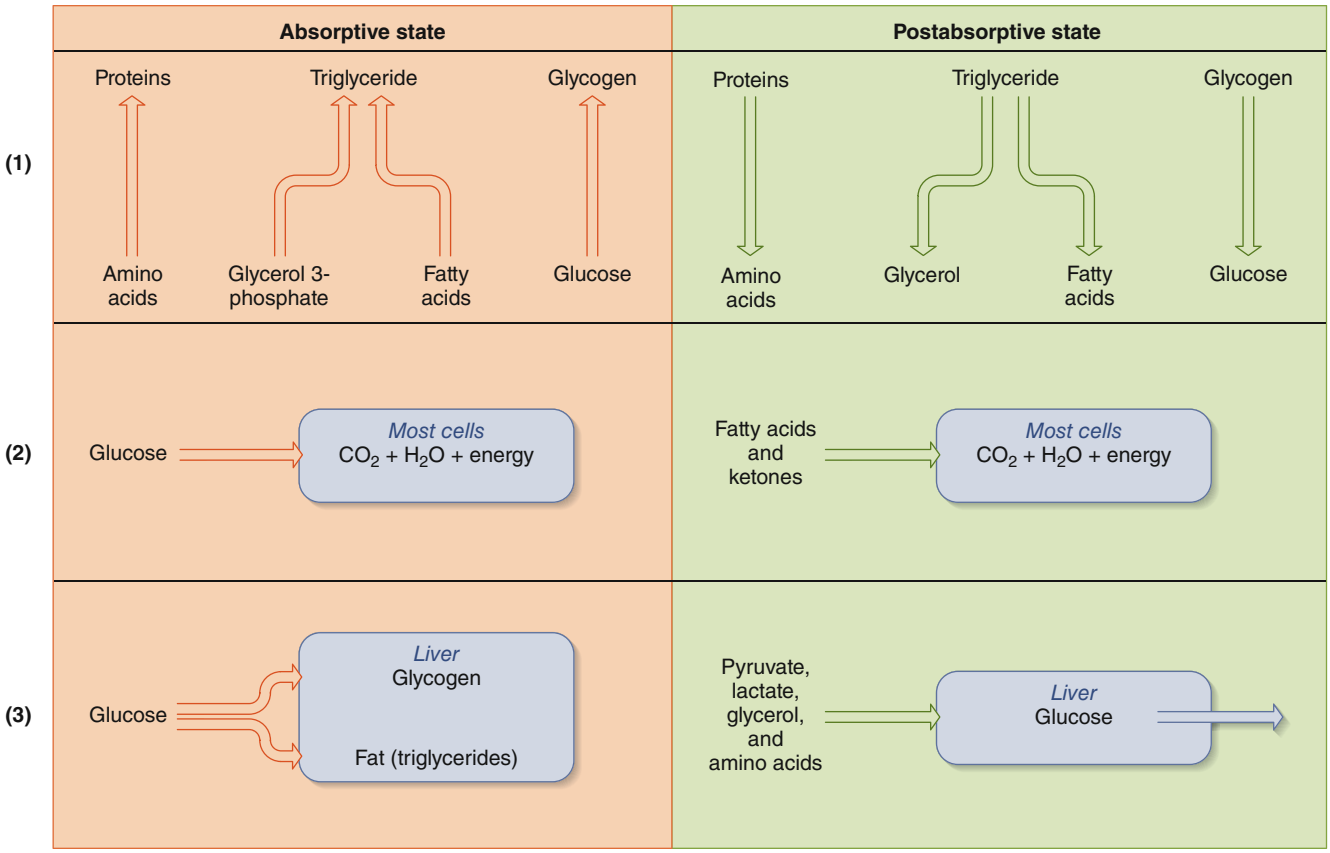


Figure 16.4 Summary of critical points in transition from the absorptive state to the postabsorptive state. The term *absorptive state* could be replaced with *actions of insulin,* and the term *postabsorptive state* with *results of decreased insulin.* The numbers at the left margin refer to discussion questions in the text.

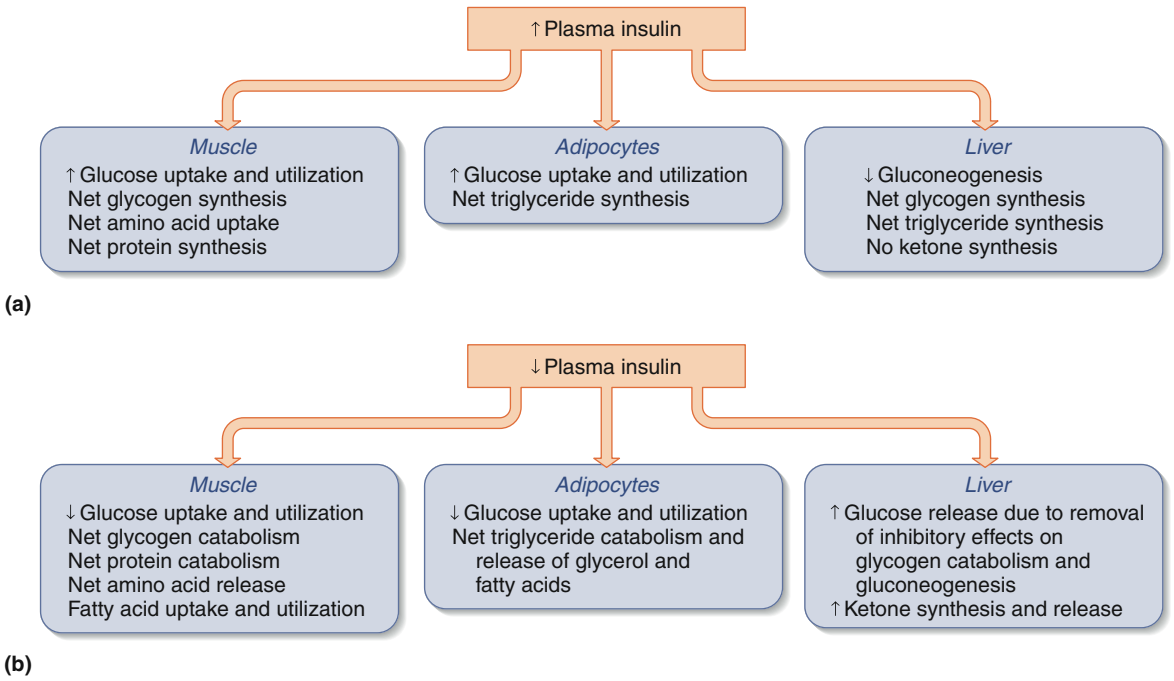
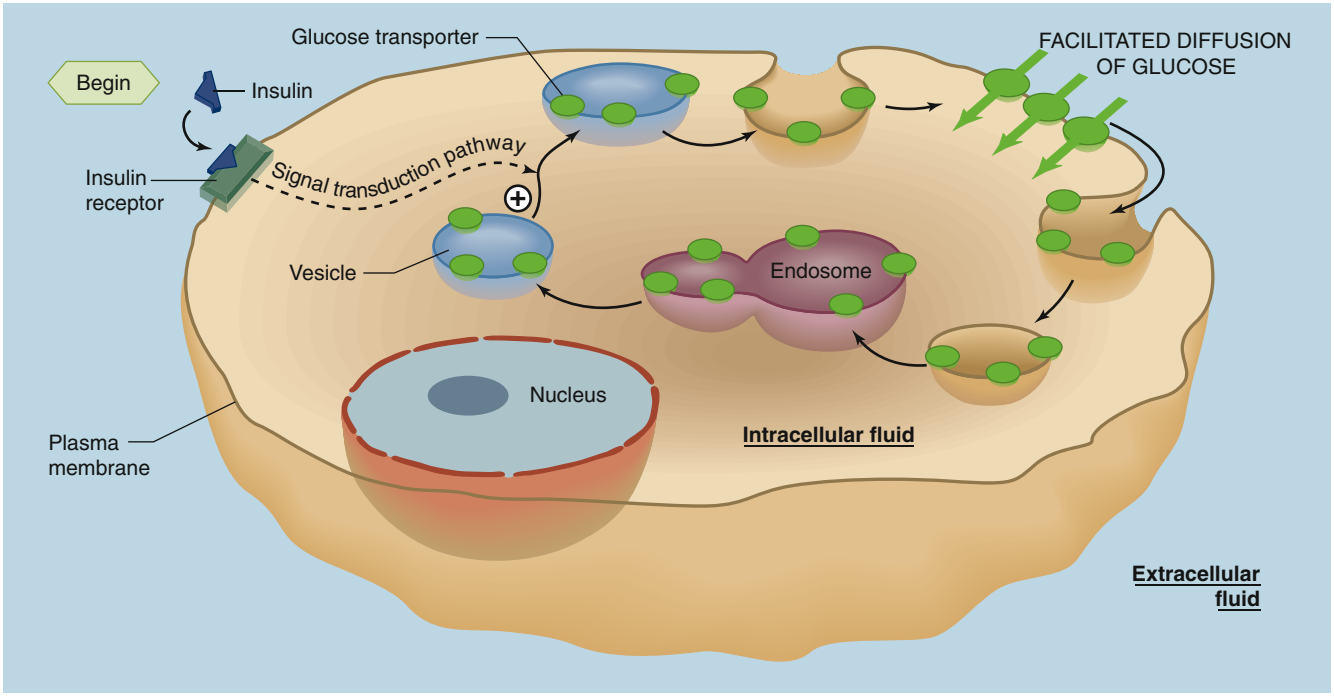


Figure 16.5 Summary of overall target-cell responses to (a) an increase or (b) a decrease in the plasma concentration of insulin. The responses in (a) are virtually identical to the absorptive-state events of Figure 16.1 and the left panel of Figure 16.4; the responses in (b) are virtually identical to the postabsorptive-state events of Figure 16.3 and the right panel of Figure 16.4.



AP|R **Figure 16.6** Stimulation by insulin of the translocation of glucose transporters from cytoplasmic vesicles to the plasma membrane in skeletal muscle cells and adipose-tissue cells. Note that these transporters are constantly recycled by endocytosis from the plasma membrane back through endosomes into vesicles. As long as insulin concentration is elevated, the entire cycle continues and the number of transporters in the plasma membrane stays high. This is how insulin decreases the plasma concentration of glucose. In contrast, when insulin concentration decreases, the cycle is broken, the vesicles accumulate in the cytoplasm, and the number of transporters in the plasma membrane decreases. Thus, without insulin, the plasma glucose concentration would increase, because glucose transport from plasma to cells would be decreased.

PHYSIOLOGICAL INQUIRY

- What advantage is there to having insulin-dependent glucose transporters already synthesized and prepackaged in a cell, even before it is stimulated by insulin?

Answer can be found at end of chapter.

and adipocytes. Of great significance is that the cells of the brain express a different subtype of GLUT, one that has very high affinity for glucose and whose activity is *not* insulin-dependent; it is always present in the plasma membranes of neurons in the brain. This ensures that even if the plasma insulin concentration is very low, as in prolonged fasting, cells of the brain can continue to take up glucose from the blood and maintain their function.

A description of the many enzymes with activities and/or concentrations that are influenced by insulin is beyond the scope of this book, but the overall pattern is shown in **Figure 16.7** for reference and to illustrate several principles. The essential information to understand about the actions of insulin is the target cells' ultimate responses (that is, the material summarized in Figure 16.5). Figure 16.7 shows some of the specific biochemical reactions that underlie these responses.

A major principle illustrated by Figure 16.7 is that, in each of its target cells, insulin brings about its ultimate responses by multiple actions. Take, for example, its effects on skeletal muscle cells. In these cells, insulin favors glycogen formation and storage by (1) increasing glucose transport into the cell, (2) stimulating the key enzyme (**glycogen synthase**) that catalyzes the rate-limiting step in glycogen synthesis, and (3) inhibiting the key enzyme (**glycogen phosphorylase**) that catalyzes glycogen catabolism. As a result, insulin favors glucose transformation to and storage as glycogen in skeletal muscle through three mechanisms. Similarly, for protein synthesis in skeletal muscle cells, insulin (1) increases the number of active plasma membrane transporters for amino acids, thereby increasing amino acid transport into the cells; (2) stimulates the ribosomal enzymes that mediate the synthesis of protein from these amino acids; and (3) inhibits the enzymes that mediate protein catabolism.

Control of Insulin Secretion

The major controlling factor for insulin secretion is the plasma glucose concentration. An increase in plasma glucose concentration, as occurs after a meal containing carbohydrate, acts on the beta cells of the islets of Langerhans to stimulate insulin secretion, whereas a decrease in plasma glucose removes the stimulus for insulin secretion. The feedback nature of this system is shown in **Figure 16.8**; following a meal, the increase in plasma glucose concentration stimulates insulin secretion. The insulin stimulates the entry of glucose into muscle and adipose tissue, as well as net uptake rather than net output of glucose by the liver. These effects subsequently decrease the blood concentration of glucose to its premeal level, thereby removing the stimulus for insulin secretion and causing it to return to its previous level. This is a classic example of a homeostatic process regulated by negative feedback.

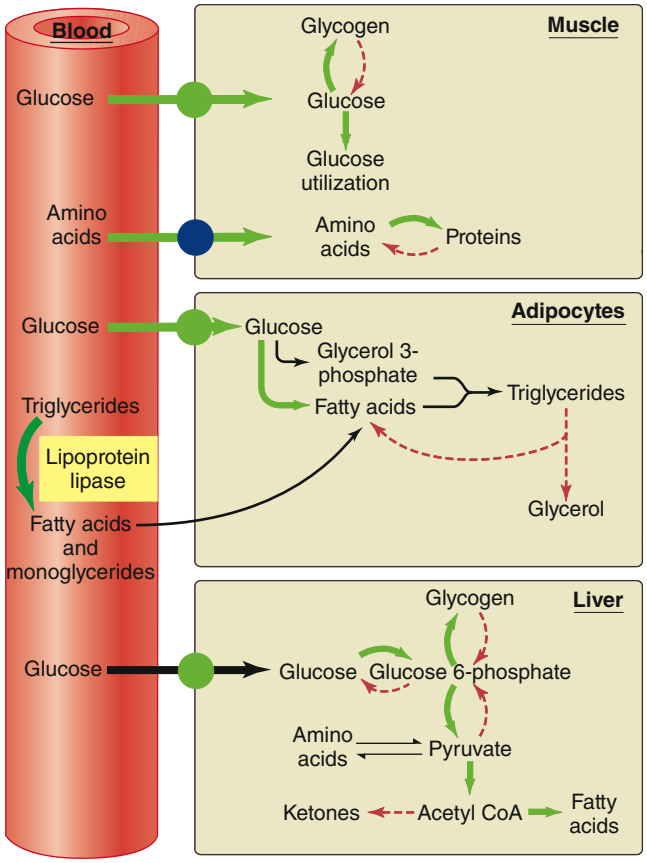
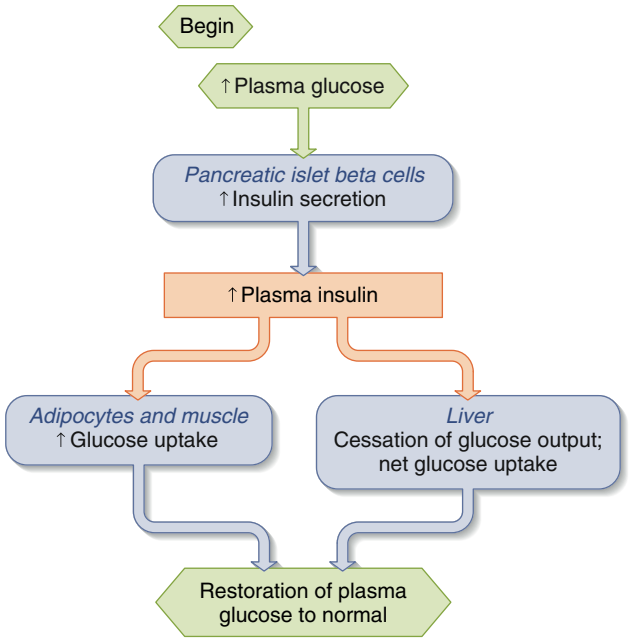


Figure 16.7 Illustration of the key biochemical events that underlie the responses of target cells to insulin as summarized in Figure 16.5. Each green arrow denotes a process stimulated by insulin, whereas a dashed red arrow denotes inhibition by insulin. Except for the effects on the transport proteins for glucose and amino acids, all other effects are exerted on insulin-sensitive enzymes. The bowed arrows denote pathways whose reversibility is mediated by different enzymes; such enzymes are commonly the ones influenced by insulin and other hormones. The black arrows are processes that are not *directly* affected by insulin but are enhanced in the presence of increased insulin as the result of mass action.

In addition to plasma glucose concentration, several other factors control insulin secretion (**Figure 16.9**). For example, increased amino acid concentrations stimulate insulin secretion. This is another negative feedback control; amino acid concentrations increase in the blood after ingestion of a protein-containing meal, and the increased plasma insulin stimulates the uptake of these amino acids by muscle and other cells, thereby lowering their concentrations.

There are also important hormonal controls over insulin secretion. For example, a family of hormones known as **incretins**—secreted by enteroendocrine cells in the gastrointestinal tract in response to eating—amplifies the insulin response to glucose. The major incretins include glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). The actions of incretins provide a feedforward component to glucose regulation during the ingestion of a meal. Consequently, insulin secretion increases more than it would if plasma glucose were the only controller, thereby minimizing the absorptive peak in plasma glucose concentration. This mechanism minimizes the likelihood of large increases in plasma glucose after a meal, which



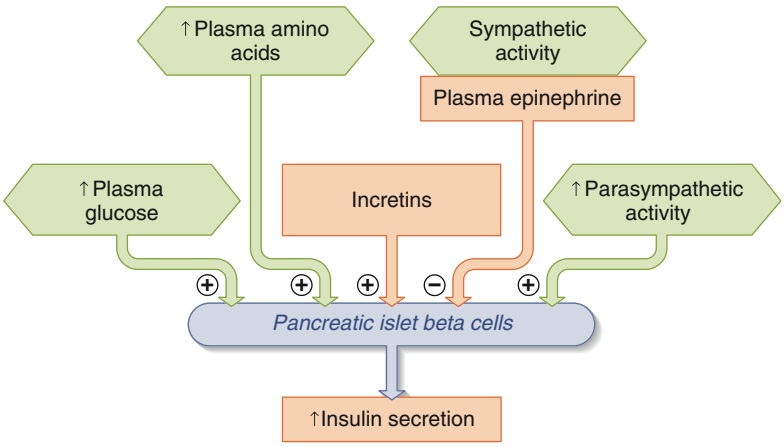
AP|R **Figure 16.8** Nature of plasma glucose control over insulin secretion. As glucose concentration increases in plasma (e.g., after a meal containing carbohydrate), insulin secretion is rapidly stimulated. The increase in insulin stimulates glucose transport from extracellular fluid into cells, thus decreasing plasma glucose concentrations. Insulin also acts to inhibit hepatic glucose output.

PHYSIOLOGICAL INQUIRY

- Notice that the brain is not insulin-sensitive. Why is that advantageous?

Answer can be found at end of chapter.

among other things could exceed the capacity of the kidneys to completely reabsorb all of the glucose that appears in the filtrate in the renal nephrons. An analog of GLP-1 is currently used for the treatment of type 2 diabetes mellitus, in which the pancreas often produces insufficient insulin and the body's cells are less



AP|R **Figure 16.9** Major controls of insulin secretion. The ⊕ and ⊖ symbols represent stimulatory and inhibitory actions, respectively. Incretins are gastrointestinal hormones that act as feedforward signals to the pancreas.

responsive to insulin. Injection of this analog before a meal may increase a person's circulating insulin concentration sufficiently to compensate for the decreased sensitivity of cells to insulin. The clinical features of the different forms of diabetes mellitus will be covered later in this chapter.

Finally, input of the autonomic neurons to the islets of Langerhans also influences insulin secretion. Activation of the parasympathetic neurons, which occurs during the ingestion of a meal, stimulates the secretion of insulin and constitutes a second type of feedforward regulation. In contrast, activation of the sympathetic neurons to the islets or an increase in the plasma concentration of epinephrine (the hormone secreted by the adrenal medulla) inhibits insulin secretion. The significance of this relationship for the body's response to low plasma glucose (hypoglycemia), stress, and exercise—all situations in which sympathetic activity is increased—will be described later in this chapter, but all of these are situations where an increase in plasma glucose concentration would be beneficial.

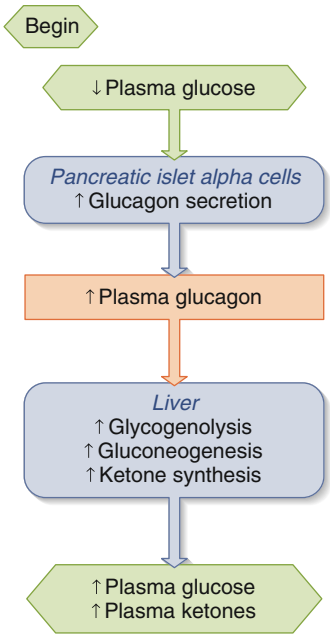
In summary, insulin has the primary function in controlling the metabolic adjustments required for feasting or fasting. Other hormonal and neural factors, however, also have significant functions. They all oppose the action of insulin in one way or another and are known as **glucose-counterregulatory controls.** As described next, the most important of these are glucagon, epinephrine, sympathetic nerves, cortisol, and growth hormone.

Glucagon

As mentioned earlier, glucagon is the polypeptide hormone produced by the alpha cells of the pancreatic islets. The major physiological effects of glucagon occur within the liver and oppose those of insulin (**Figure 16.10**). Thus, glucagon (1) stimulates glycogenolysis, (2) stimulates gluconeogenesis, and (3) stimulates the synthesis of ketones. The overall results are to increase the plasma concentrations of glucose and ketones, which are important for the postabsorptive state, and to prevent hypoglycemia. The effects, if any, of glucagon on adipocyte function in humans are still unresolved.

The major stimulus for glucagon secretion is a decrease in the circulating concentration of glucose (which in turn causes a decrease in plasma insulin). The adaptive value of such a reflex is clear; a decreased plasma glucose concentration induces an increase in the secretion of glucagon into the blood, which, by its effects on metabolism, serves to restore normal blood glucose concentration by glycogenolysis and gluconeogenesis. At the same time, glucagon supplies ketones for utilization by the brain. Conversely, an increased plasma glucose concentration inhibits the secretion of glucagon, thereby helping to return the plasma glucose concentration toward normal. As a result, during the postabsorptive state, there is an increase in the glucagon/insulin ratio in the plasma, and this accounts almost entirely for the transition from the absorptive to the postabsorptive state. The dual and opposite actions of glucagon and insulin on glucose homeostasis clearly illustrate the general principle of physiology that most physiological functions are controlled by multiple regulatory systems, often working in opposition.

The secretion of glucagon, like that of insulin, is controlled not only by the plasma concentration of glucose but also by amino acids and by neural and hormonal inputs to the islets. For example, significant increases in certain amino acids—as may occur after a meal rich in protein—stimulate an increase in plasma glucagon. Recall that amino acids also stimulate insulin secretion. Glucagon secreted in such situations helps prevent hypoglycemia that may occur following the increase in insulin in a protein-rich meal. As another example, the sympathetic nerves to the islets stimulate glucagon secretion—just the opposite of their effect on insulin secretion. Glucagon, then, is part of the fight-or-flight responses you have learned about in earlier chapters. This is one way in which additional energy in the form of glucose is provided in times of stress or emergency.



AP|R **Figure 16.10** Nature of plasma glucose control over glucagon secretion.

PHYSIOLOGICAL INQUIRY

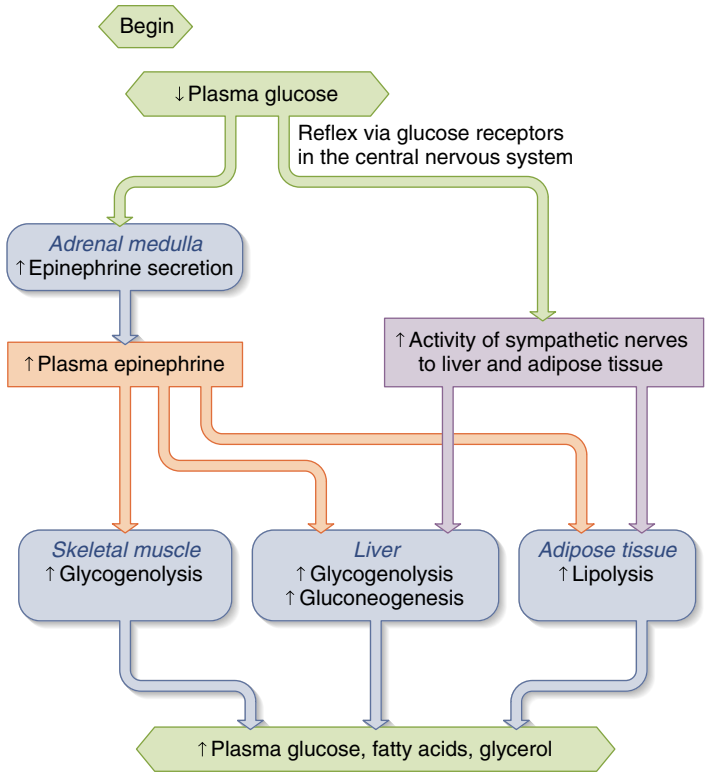
- Given the effects of glucagon on plasma glucose concentrations, what effect do you think fight-or-flight (stress) reactions would have on the circulating level of glucagon?

Answer can be found at end of chapter.

Epinephrine and Sympathetic Nerves to Liver and Adipose Tissue

As noted earlier, epinephrine and the sympathetic nerves to the pancreatic islets inhibit insulin secretion and stimulate glucagon secretion. In addition, epinephrine also affects nutrient metabolism directly (**Figure 16.11**). Its major direct effects include stimulation of (1) glycogenolysis in both the liver and skeletal muscle, (2) gluconeogenesis in the liver, and (3) lipolysis in adipocytes. Activation of the sympathetic nerves to the liver and adipose tissue elicits the same responses from these organs as does circulating epinephrine.

In adipocytes, epinephrine stimulates the activity of an enzyme called **hormone-sensitive lipase** (**HSL**)**.** Once activated, HSL works along with other enzymes to catalyze the breakdown of triglycerides to free fatty acids and glycerol. Both are then released into the blood, where they serve directly as an energy



AP|R **Figure 16.11** Participation of the sympathetic nervous system in the response to a low plasma glucose concentration (hypoglycemia). Glycogenolysis in skeletal muscle contributes to restoring plasma glucose by releasing lactate, which is converted to glucose in the liver and released into the blood. Recall also from Figure 16.9 and the text that the sympathetic nervous system inhibits insulin and stimulates glucagon secretion, which further contributes to the increased plasma energy sources.

source (fatty acids) or as a gluconeogenic precursor (glycerol). Not surprisingly, insulin inhibits the activity of HSL during the absorptive state, because it would not be beneficial to break down stored fat when the blood is receiving nutrients from ingested food. Thus, enhanced sympathetic nervous system activity exerts effects on organic metabolism—specifically, increased plasma concentrations of glucose, glycerol, and fatty acids—that are opposite those of insulin.

As might be predicted from these effects, low blood glucose leads to increases in both epinephrine secretion and sympathetic nerve activity to the liver and adipose tissue. This is the same stimulus that leads to increased glucagon secretion, although the receptors and pathways are totally different. When the plasma glucose concentration decreases, glucose-sensitive cells in the central nervous system (and, possibly, the liver) initiate the reflexes that lead to increased activity in the sympathetic pathways to the adrenal medulla, liver, and adipose tissue. The adaptive value of the response is the same as that for the glucagon response to hypoglycemia; blood glucose returns toward normal, and fatty acids are supplied for cell utilization.

Cortisol

Cortisol, the major glucocorticoid produced by the adrenal cortex, has an essential permissive function in the adjustments to fasting. We have described how fasting is associated with the stimulation of both gluconeogenesis and lipolysis; however, neither of these critical metabolic transformations occurs to the usual degree in a person deficient in cortisol. In other words, the plasma cortisol concentration does not need to increase much during fasting, but the presence of cortisol in the blood maintains the concentrations of the key liver and adipose-tissue enzymes required for gluconeogenesis and lipolysis—for example, HSL. Therefore, in response to fasting, individuals with a cortisol deficiency can develop hypoglycemia significant enough to interfere with cellular function. Moreover, cortisol can have more than a permissive function when its plasma concentration does increase, as it does during stress. At high concentrations, cortisol elicits many metabolic events ordinarily associated with fasting (**Table 16.3**). In fact, cortisol actually decreases the sensitivity of muscle and adipose cells to insulin, which helps to maintain plasma glucose concentration during fasting, thereby providing a regular source of energy for the brain. Clearly, here is another hormone that, in addition to glucagon and epinephrine, can exert actions opposite those of insulin. Indeed, individuals with pathologically high plasma concentrations of cortisol or who are treated with synthetic glucocorticoids for medical reasons can develop symptoms similar to those seen in individuals, such as those with type 2 diabetes mellitus, whose cells do not respond adequately to insulin.

Growth Hormone

The primary physiological effects of growth hormone are to stimulate both growth and protein synthesis. Compared to these effects, those it exerts on carbohydrate and lipid metabolism are less significant. Nonetheless, as is true for cortisol, either deficiency or excess of growth hormone does produce significant abnormalities in lipid and carbohydrate metabolism. Growth hormone's effects on these nutrients, in contrast to those on protein metabolism, are similar to those of cortisol and opposite those of insulin. Growth hormone (1) increases the responsiveness of adipocytes to lipolytic stimuli, (2) stimulates gluconeogenesis by the liver, and (3) reduces the ability of insulin to stimulate glucose uptake by muscle and adipose tissue. These three effects are often termed growth hormone's "anti-insulin effects." Because of these effects, some of the symptoms observed in individuals with acromegaly (excess growth hormone production; see the Chapter 11 Clinical Case Study) are similar to those observed in people with insulin resistance due to type 2 diabetes mellitus.

TABLE 16.3 Effects of Cortisol on Organic Metabolism

I. Basal concentrations are permissive for stimulation of gluconeogenesis and lipolysis in the postabsorptive state.

II. Increased plasma concentrations cause:
- A. increased protein catabolism.
- B. increased gluconeogenesis.
- C. decreased glucose uptake by muscle cells and adipose-tissue cells.
- D. increased triglyceride breakdown.

Net result: Increased plasma concentrations of amino acids, glucose, and free fatty acids

TABLE 16.4 Summary of Glucose-Counterregulatory Controls*

	Glucagon	Epinephrine	Cortisol	Growth Hormone
Glycogenolysis	✓	✓		
Gluconeogenesis	✓	✓	✓	✓
Lipolysis		✓	✓	✓
Inhibition of glucose uptake by muscle cells and adipose tissue cells			✓	✓

*A ✓ indicates that the hormone stimulates the process; no ✓ indicates that the hormone has no major physiological effect on the process. Epinephrine stimulates glycogenolysis in both liver and skeletal muscle, whereas glucagon does so only in liver.

A summary of the counterregulatory control of metabolism is given in Table 16.4.

Hypoglycemia

Hypoglycemia is broadly defined as an abnormally low plasma glucose concentration. The plasma glucose concentration can decrease to very low values, usually during the postabsorptive state, in persons with several types of disorders. ***Fasting hypoglycemia*** and the relatively uncommon disorders responsible for it can be understood in terms of the regulation of blood glucose concentration. They include (1) an excess of insulin due to an insulin-producing tumor, drugs that stimulate insulin secretion, or taking too much insulin (if the person is diabetic); and (2) a defect in one or more glucose-counterregulatory controls, for example, inadequate glycogenolysis and/or gluconeogenesis due to liver disease or cortisol deficiency.

Fasting hypoglycemia causes many symptoms. Some—increased heart rate, trembling, nervousness, sweating, and anxiety—are accounted for by activation of the sympathetic nervous system caused reflexively by the hypoglycemia. Other symptoms, such as headache, confusion, dizziness, loss of coordination, and slurred speech, are direct consequences of too little glucose reaching neurons of the brain. More serious neurological effects, including convulsions and coma, can occur if the plasma glucose decreases to very low concentrations.

16.3 Energy Homeostasis in Exercise and Stress

During exercise, large quantities of fuels must be mobilized to provide the energy required for skeletal and cardiac muscle contraction. These include plasma glucose and fatty acids as well as the muscle's own glycogen.

The additional plasma glucose used during exercise is supplied by the liver, both by breakdown of its glycogen stores and by gluconeogenesis. Glycerol is made available to the liver by a large increase in adipose-tissue lipolysis due to activation of HSL, with a resultant release of glycerol and fatty acids into the blood; the fatty acids serve as an additional energy source for the exercising muscle.

What happens to the plasma glucose concentration during exercise? It changes very little in short-term, mild-to-moderate exercise and may even increase slightly with strenuous, short-term activity due to the counterregulatory actions of hormones. However, during prolonged exercise (Figure 16.12)—more than about 90 min—the plasma glucose concentration does decrease but usually by less than 25%. Clearly, glucose output by the liver increases approximately in proportion to increased glucose utilization during exercise, at least until the later stages of prolonged exercise when it begins to lag somewhat.

The metabolic profile of an exercising person—increases in hepatic glucose production, triglyceride breakdown, and fatty acid utilization—is similar to that of a fasting person, and the endocrine controls are also the same. Exercise is characterized by a decrease in insulin secretion and an increase in glucagon secretion (see Figure 16.12), and the changes in the plasma concentrations of these two hormones are the major controls during exercise. In addition, activity of the sympathetic nervous system increases (including secretion of epinephrine) and cortisol and growth hormone secretion both increase as well.

What triggers increased glucagon secretion and decreased insulin secretion during exercise? One signal, at least during *prolonged* exercise, is the modest decrease in plasma glucose that occurs (see Figure 16.12). This is the same signal that controls the secretion of these hormones in fasting. Other inputs at all

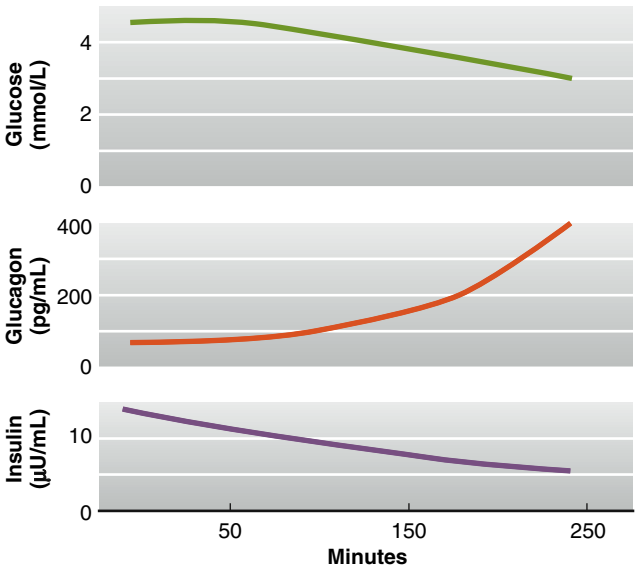


Figure 16.12 Plasma concentrations of glucose, glucagon, and insulin during prolonged (240 min) moderate exercise at a fixed intensity (pg/mL = Picograms per milliliter; μU/mL = Microunits per milliliter). Source: Adapted from Felig, P., and J. Wahren: *New England Journal of Medicine*, **293**:1078 (1975).

intensities of exercise include increased circulating epinephrine and increased activity of the sympathetic neurons supplying the pancreatic islets. Thus, the increased sympathetic nervous system activity characteristic of exercise not only contributes directly to energy mobilization by acting on the liver and adipose tissue but contributes indirectly by inhibiting the secretion of insulin and stimulating that of glucagon. This sympathetic output is not triggered by changes in plasma glucose concentration but is mediated by the central nervous system as part of the neural response to exercise.

One component of the response to exercise is quite different from the response to fasting; in exercise, glucose uptake and utilization by the skeletal and cardiac muscles are increased, whereas during fasting they are markedly decreased. How is it that, during exercise, the movement of glucose via facilitated diffusion into skeletal muscle can remain high in the presence of decreased plasma insulin and increased plasma concentrations of cortisol and growth hormone, all of which decrease glucose uptake by skeletal muscle? By an as-yet-unidentified mechanism, muscle contraction causes migration of an intracellular store of glucose transporters to the plasma membrane and an increase in synthesis of the transporters. For this reason, even though exercising muscles require more glucose than do muscles at rest, less insulin is required to induce glucose transport into muscle cells. We will see later that this mechanism is an important factor that explains why exercise is an effective therapy for type 2 diabetes mellitus.

Exercise and the postabsorptive state are not the only situations characterized by the endocrine profile of decreased insulin and increased glucagon, sympathetic activity, cortisol, and growth hormone. This profile also occurs in response to a variety of nonspecific stresses, both physical and emotional. The adaptive value of these endocrine responses to stress is that the resulting metabolic shifts prepare the body for physical activity (fight or flight) in the face of real or threatened challenges to homeostasis. In addition, the amino acids liberated by the catabolism of body protein stores because of decreased insulin and increased cortisol not only provide energy via gluconeogenesis but also constitute a potential source of amino acids for tissue repair should injury occur.

Chronic, intense exercise can also be stressful for the human body. In such cases, certain nonessential functions decrease significantly so that nutrients can be directed primarily to the CNS and to muscle. One of these nonessential functions is reproduction. Consequently, adolescents engaged in rigorous daily training regimens, such as Olympic-caliber gymnasts, may show delayed puberty. Similarly, women who perform chronic, intense exercise may become temporarily infertile, a condition known as ***exercise-induced amenorrhea*** (the lack of regular menstrual cycles—see Chapter 17). This condition occurs in a variety of occupations that combine weight loss and strenuous exercise, such as may occur in professional ballerinas. Whether exercise-induced infertility occurs in men is uncertain, but most evidence suggests it does not.

SECTION A SUMMARY

Events of the Absorptive and Postabsorptive States

I. During absorption, energy is provided primarily by absorbed carbohydrate. Net synthesis of glycogen, triglyceride, and protein occurs.
   a. Some absorbed carbohydrate not used for energy is converted to glycogen, mainly in the liver and skeletal muscle, but most is converted in liver and adipocytes to glycerol 3-phosphate and fatty acids, which then combine to form triglycerides. The liver releases its triglycerides in very-low-density lipoproteins, the fatty acids of which are picked up by adipocytes.
   b. The fatty acids of some absorbed triglycerides are used for energy, but most are rebuilt into fat in adipose tissue.
   c. Plasma cholesterol is a precursor for the synthesis of plasma membranes, bile salts, and steroid hormones.
   d. Cholesterol synthesis by the liver is controlled so as to homeostatically regulate plasma cholesterol concentration; it varies inversely with ingested cholesterol.
   e. The liver also secretes cholesterol into the bile and converts it to bile salts.
   f. Plasma cholesterol is carried mainly by low-density lipoproteins, which deliver it to cells; high-density lipoproteins carry cholesterol from cells to the liver and steroid-producing cells. The LDL/HDL ratio correlates with the incidence of heart disease.
   g. Most absorbed amino acids are converted to proteins, but excess amino acids are converted to carbohydrate and fat.
   h. There is a net uptake of glucose by the liver.

II. In the postabsorptive state, the concentration of glucose in the blood is maintained by a combination of glucose production by the liver and a switch from glucose utilization to fatty acid and ketone utilization by most tissues.
   a. Synthesis of glycogen, fat, and protein is curtailed, and net breakdown of these molecules occurs.
   b. The liver forms glucose by glycogenolysis of its own glycogen and by gluconeogenesis from lactate and pyruvate (from the breakdown of muscle glycogen), glycerol (from adipose-tissue lipolysis), and amino acids (from protein catabolism).
   c. Glycolysis is decreased, and most of the body's energy supply comes from the oxidation of fatty acids released by adipose-tissue lipolysis and of ketones produced from fatty acids by the liver.
   d. The brain continues to use glucose but also starts using ketones as they build up in the blood.

Endocrine and Neural Control of the Absorptive and Postabsorptive States

I. The major hormones secreted by the pancreatic islets of Langerhans are insulin by the beta cells and glucagon by the alpha cells.

II. Insulin is the most important hormone controlling metabolism.
   a. In muscle, it stimulates glucose uptake, glycolysis, and net synthesis of glycogen and protein. In adipose tissue, it stimulates glucose uptake and net synthesis of triglyceride. In liver, it inhibits gluconeogenesis and glucose release and stimulates the net synthesis of glycogen and triglycerides.
   b. The major stimulus for insulin secretion is an increased plasma glucose concentration, but secretion is also influenced by many other factors, which are summarized in Figure 16.9.

III. Glucagon, epinephrine, cortisol, and growth hormone all exert effects on carbohydrate and lipid metabolism that are opposite, in one way or another, to those of insulin. They increase plasma concentrations of glucose, glycerol, and fatty acids.
   a. Glucagon's physiological actions are on the liver, where glucagon stimulates glycogenolysis, gluconeogenesis, and ketone synthesis.
   b. The major stimulus for glucagon secretion is hypoglycemia, but secretion is also stimulated by other inputs, including the sympathetic nerves to the islets.
   c. Epinephrine released from the adrenal medulla in response to hypoglycemia stimulates glycogenolysis in the liver and muscle, gluconeogenesis in the liver, and lipolysis in adipocytes. The

sympathetic nerves to liver and adipose tissue exert effects similar to those of epinephrine.

d. Cortisol is permissive for gluconeogenesis and lipolysis; in higher concentrations, it stimulates gluconeogenesis and blocks glucose uptake. These last two effects are also exerted by growth hormone.

IV. Hypoglycemia is defined as an abnormally low glucose concentration in the blood. Symptoms of hypoglycemia are similar to those of sympathetic nervous system activation. However, severe hypoglycemia can lead to brain dysfunction and even death if untreated.

Energy Homeostasis in Exercise and Stress

I. During exercise, the muscles use as their energy sources plasma glucose, plasma fatty acids, and their own glycogen.
   a. Glucose is provided by the liver, and fatty acids are provided by adipose-tissue lipolysis.
   b. The changes in plasma insulin, glucagon, and epinephrine are similar to those that occur during the postabsorptive state and are mediated mainly by the sympathetic nervous system.

II. Stress causes hormonal changes similar to those caused by exercise.

SECTION A REVIEW QUESTIONS

1. Using a diagram, summarize the events of the absorptive state.
2. In what two organs does major glycogen storage occur?
3. How do the liver and adipose tissue metabolize glucose during the absorptive state?
4. How does adipose tissue metabolize absorbed triglyceride, and what are the three major sources of the fatty acids in adipose-tissue triglyceride?
5. Using a diagram, describe the sources of cholesterol gain and loss. Include the functions of the liver in cholesterol metabolism, and describe the controls over these processes.
6. What are the effects of saturated and unsaturated fatty acids on plasma cholesterol?
7. What is the significance of the ratio of LDL cholesterol to HDL cholesterol?
8. What are the fates of most of the absorbed amino acids when a high-protein meal is ingested?
9. Using a diagram, summarize the events of the postabsorptive state; include the four sources of blood glucose and the pathways leading to ketone formation.
10. Distinguish between the roles of glycerol and free fatty acids during fasting.
11. List the overall responses of muscle, adipose tissue, and liver to insulin. What effects occur when the plasma insulin concentration decreases?
12. Describe several inputs controlling insulin secretion and the physiological significance of each.
13. List the effects of glucagon on the liver and their consequences.
14. Discuss two inputs controlling glucagon secretion and the physiological significance of each.
15. List the metabolic effects of epinephrine and the sympathetic nerves to the liver and adipose tissue, and state the net results of each.
16. Describe the permissive effects of cortisol and the effects that occur when plasma cortisol concentration increases.
17. List the effects of growth hormone on carbohydrate and lipid metabolism.
18. Which hormones stimulate gluconeogenesis? Glycogenolysis in the liver? Lipolysis in adipose tissue? Which hormone or hormones inhibit glucose uptake into cells?
19. Describe how plasma glucose, insulin, glucagon, and epinephrine concentrations change during exercise and stress. What causes the changes in the concentrations of the hormones?

SECTION A KEY TERMS

16.1 Events of the Absorptive and Postabsorptive States

absorptive state
α-keto acids
cholesterol
gluconeogenesis
glucose sparing
glycogenolysis
high-density lipoproteins (HDLs)
ketones
lipolysis
lipoprotein lipase
lipoproteins
low-density lipoproteins (LDLs)
postabsorptive state
very-low-density lipoproteins (VLDLs)

16.2 Endocrine and Neural Control of the Absorptive and Postabsorptive States

glucagon
glucose-counterregulatory controls
glycogen phosphorylase
glycogen synthase
hormone-sensitive lipase (HSL)
hypoglycemia
incretins
insulin
islets of Langerhans

SECTION A CLINICAL TERMS

16.1 Events of the Absorptive and Postabsorptive States

atherosclerosis
familial hypercholesterolemia

16.2 Endocrine and Neural Control of the Absorptive and Postabsorptive States

fasting hypoglycemia

16.3 Energy Homeostasis in Exercise and Stress

exercise-induced amenorrhea

SECTION B
Regulation of Total-Body Energy Balance and Temperature

16.4 General Principles of Energy Expenditure

The breakdown of organic molecules liberates some of the energy locked in their chemical bonds. Cells use this energy to perform the various forms of biological work, such as muscle contraction, active transport, and molecular synthesis. These processes illustrate the general principle of physiology that physiological processes are dictated by the laws of chemistry and physics. The first law of thermodynamics states that energy can be neither created nor destroyed but can be converted from one form to another. Therefore, internal energy liberated (ΔE) during breakdown of an

organic molecule can either appear as heat (H) or be used to perform work (W).

$$\Delta E = H + W$$

During metabolism, about 60% of the energy released from organic molecules appears immediately as heat, and the rest is used for work. The energy used for work must first be incorporated into molecules of ATP. The subsequent breakdown of ATP serves as the immediate energy source for the work. The body is incapable of converting heat to work, but the heat released in its chemical reactions helps to maintain body temperature.

Biological work can be divided into two general categories: (1) **external work**—the movement of external objects by contracting skeletal muscles; and (2) **internal work**—all other forms of work, including skeletal muscle activity not used in moving external objects. As just stated, much of the energy liberated from nutrient catabolism appears immediately as heat. What may not be obvious is that internal work, too, is ultimately transformed to heat except during periods of growth. For example, internal work is performed during cardiac contraction, but this energy appears ultimately as heat generated by the friction of blood flow through the blood vessels.

Thus, the total energy liberated when cells catabolize organic nutrients may be transformed into body heat, can be used to do external work, or can be stored in the body in the form of organic molecules. The **total energy expenditure** of the body is therefore given by the equation

Total energy expenditure = Internal heat produced
+ External work performed + Energy stored

Metabolic Rate

The basic metric unit of energy is the joule. When quantifying the energy of metabolism, however, another unit is used, called the **calorie** (equal to 4.184 joules). One calorie is the amount of heat required to raise the temperature of one gram of water from 14.5°C to 15.5°C. Because the amount of energy stored in food is quite high relative to a calorie, a more convenient expression of energy in this context is the **kilocalorie** (**kcal**), which is equal to 1000 calories. (In the field of nutrition, it is common to use the terms *calorie* and *kilocalorie* as synonyms, even though this is incorrect. We will adhere to scientific convention in this text and refer strictly to *kilocalories*.) Total energy expenditure per unit time is called the **metabolic rate.**

Because many factors cause the metabolic rate to vary (**Table 16.5**), the most common method for evaluating it specifies certain standardized conditions and measures what is known as the **basal metabolic rate** (**BMR**). In the basal condition, the subject is at rest in a room at a comfortable temperature and has not eaten for at least 12 h (i.e., is in the postabsorptive state). These conditions are arbitrarily designated "basal," even though the metabolic rate during sleep may be lower than the BMR. The BMR is sometimes called the "metabolic cost of living," and most of the energy involved is expended by the heart, muscle, liver, kidneys, and brain. For the following discussion, the term BMR can be applied to metabolic rate only when the specified conditions are met. The next sections describe several of the important determinants of BMR and metabolic rate.

Thyroid Hormone

The active thyroid hormone, T_3, is the most important determinant of BMR regardless of body size, age, or gender. T_3 increases the oxygen consumption and heat production of most body tissues, a notable exception being the brain. This ability to increase BMR is known as a **calorigenic effect.**

Long-term excessive T_3, as in people with hyperthyroidism (see Chapter 11 and the first case study in Chapter 19), induce a host of effects secondary to the calorigenic effect. For example, the increased metabolic demands markedly increase hunger and food intake. The greater intake often remains inadequate to

TABLE 16.5 Some Factors Affecting the Metabolic Rate

Sleep (decreased during sleep)	
Age (decreased with increasing age)	
Gender (women typically lower rate than men at any given size)	
Fasting (BMR decreases, which conserves energy stores)	
Height, weight, and body surface area	
Growth	The presence of, or an increase in, any of these factors causes an increase in metabolic rate
Pregnancy, menstruation, lactation	
Infection or other disease	
Body temperature	
Recent ingestion of food	
Muscular activity	
Emotional stress	
Environmental temperature	
Circulating concentrations of various hormones, especially epinephrine, thyroid hormone, and leptin	

meet metabolic demands. The resulting net catabolism of protein and fat stores leads to loss of body weight. Also, the greater heat production activates heat-dissipating mechanisms, such as skin vasodilation and sweating, and the person feels intolerant to warm environments. In contrast, the hypothyroid person may experience cold intolerance.

Epinephrine Epinephrine is another hormone that exerts a calorigenic effect. This effect may be related to its stimulation of glycogen and triglyceride catabolism, as ATP hydrolysis and energy liberation occur during both the breakdown and subsequent resynthesis of these molecules. As a result, when plasma epinephrine increases significantly as a result of autonomic stimulation of the adrenal medulla, the metabolic rate increases.

Diet-Induced Thermogenesis The ingestion of food increases the metabolic rate by 10% to 20% for a few hours after eating. This effect is known as **diet-induced thermogenesis.** Ingested protein produces the greatest effect. Most of the increased heat production is caused by the processing of the absorbed nutrients by the liver, the energy expended by the gastrointestinal tract in digestion and absorption, and the storage of energy in adipose and other tissue. Because of the contribution of diet-induced thermogenesis, a BMR measurement is performed in the postabsorptive state. As we will see, *prolonged* alterations in food intake (either increased or decreased total calories) also have significant effects on metabolic rate.

Muscle Activity The factor that can increase metabolic rate the most is increased skeletal muscle activity. Even minimal increases in muscle contraction significantly increase metabolic rate, and strenuous exercise may increase energy expenditure several-fold (**Figure 16.13**). Therefore, depending on the degree of physical activity, total energy expenditure may vary for a healthy young adult from a value of approximately 1500 kcal/24 h (for a sedentary individual) to more than 7000 kcal/24 h (for someone who is extremely active). Changes in muscle activity also account in part for the changes in metabolic rate that occur during specific phases of sleep (decreased muscle contraction) and during exposure to a low environmental temperature (increased muscle contraction due to shivering).

Approximate Energy Expenditure During Different Types of Activity for a 70 kg (154 lb) Person

Form of Activity	Energy kcal/h
Sitting at rest	100
Walking on level ground at 4.3 km/h (2.6 mi/h)	200
Weight lifting *(light workout)*	220
Bicycling on level ground at 9 km/h (5.3 mi/h)	300
Walking on 3% grade at 4.3 km/h (2.6 mi/h)	360
Shoveling snow	480
Jogging at 9 km/h (5.3 mi/h)	570
Rowing at 20 strokes/ min	830

Figure 16.13 Approximate rates of energy expenditure for a variety of common activities.

16.5 Regulation of Total-Body Energy Stores

Under normal conditions, for body weight to remain stable, the total energy expenditure (metabolic rate) of the body must equal the total energy intake. We have already identified the ultimate forms of energy expenditure: internal heat production, external work, and net molecular synthesis (energy storage). The source of input is the energy contained in ingested food. Therefore,

$$\text{Energy from food intake} = \text{Internal heat produced} + \text{External work} + \text{Energy stored}$$

This equation includes no term for loss of energy from the body via excretion of nutrients because normally only negligible losses occur via the urine, feces, and sloughed hair and skin. In certain diseases, however, the most important being diabetes mellitus, urinary losses of organic molecules may be quite large and would have to be included in the equation.

Rearranging the equation to focus on energy storage gives

$$\text{Energy stored} = \text{Energy from food intake} - (\text{Internal heat produced} + \text{External work})$$

Consequently, whenever energy intake differs from the sum of internal heat produced and external work, changes in energy storage occur; that is, the total-body energy content increases or decreases. Energy storage is mainly in the form of fat in adipose tissue.

It is worth emphasizing at this point that "body weight" and "total-body energy content" are not synonymous. Body weight is determined not only by the amount of fat, carbohydrate, and protein in the body but also by the amounts of water, bone, and other minerals. For example, an individual can lose body weight quickly as the result of sweating or an excessive increase in urinary output. It is also possible to gain large amounts of weight as a result of water retention, as occurs, for example, during heart failure. Moreover, even focusing only on the nutrients, a constant body weight does not mean that total-body energy content is constant. The reason is that 1 g of fat contains 9 kcal, whereas 1 g of either carbohydrate or protein contains 4 kcal. Aging, for example, is usually associated with a gain of fat and a loss of protein; the result is that even though the person's body weight may stay constant, the total-body energy content has increased. Apart from these qualifications, however, in the remainder of this chapter, changes in body weight are equated with changes in total-body energy content and, more specifically, changes in body fat stores.

Body weight in adults is usually regulated around a stable set point. Theoretically, this regulation can be achieved by reflexively adjusting caloric intake and/or energy expenditure in response to changes in body weight. It was once assumed that regulation of caloric intake was the only important adjustment, and the next section will describe this process. However, it is now clear that energy expenditure can also be adjusted in response to changes in body weight.

A typical demonstration of this process in human beings follows. Total daily energy expenditure was measured in nonobese subjects at their usual body weight and again after they either lost 10% of their body weight by underfeeding or gained 10% by overfeeding. At their new body weight, the overfed subjects manifested a large (15%) increase in both resting and nonresting energy expenditure, and the underfed subjects showed a similar decrease. These changes in energy expenditure were much greater than could be accounted for simply by the altered metabolic mass of the body or having to move a larger or smaller body.

The generalization that emerges is that a dietary-induced change in total-body energy stores triggers, in negative feedback fashion, an alteration in energy expenditure that opposes the gain or loss of energy stores. This phenomenon helps explain why some dieters lose about 5 to 10 pounds fairly easily and then become stuck at a plateau.

Control of Food Intake

The control of food intake can be analyzed in the same way as any other biological control system. As the previous section emphasized, the variable being maintained in this system is total-body energy content or, more specifically, total fat stores. An essential component of such a control system is the polypeptide hormone **leptin,** synthesized by adipocytes and released from the cells in proportion to the amount of fat they contain. This hormone acts on the hypothalamus to cause a decrease in food intake, in part by inhibiting the release of **neuropeptide Y,** a hypothalamic neurotransmitter that stimulates appetite. Leptin also increases BMR and, therefore, has an important function in the changes in energy expenditure that occur in response to overfeeding or underfeeding, as described in the previous section. Thus, as illustrated in **Figure 16.14**, leptin functions in a negative feedback system to maintain a stable total-body energy content by signaling to the brain how much fat is stored.

It should be emphasized that leptin is important for *long-term* matching of caloric intake to energy expenditure. In addition, it is thought that various other signals act on the hypothalamus (and other brain areas) over short periods of time to regulate individual meal length and frequency (**Figure 16.15**). These satiety signals (factors that decrease appetite) cause the person to cease feeling hungry and set the time period before hunger returns. For example, the rate of insulin-dependent glucose utilization by certain areas of the hypothalamus increases during eating, and this probably constitutes a satiety signal. Insulin, which increases during food absorption, also acts as a direct satiety signal. Diet-induced thermogenesis tends to increase body temperature slightly, which acts as yet another satiety signal. Finally, some satiety signals are initiated by the presence of food within the gastrointestinal tract. These include neural signals triggered by stimulation of both stretch receptors and chemoreceptors in the stomach and duodenum, as well as by certain of the hormones (cholecystokinin, for example) released from the stomach and duodenum during eating.

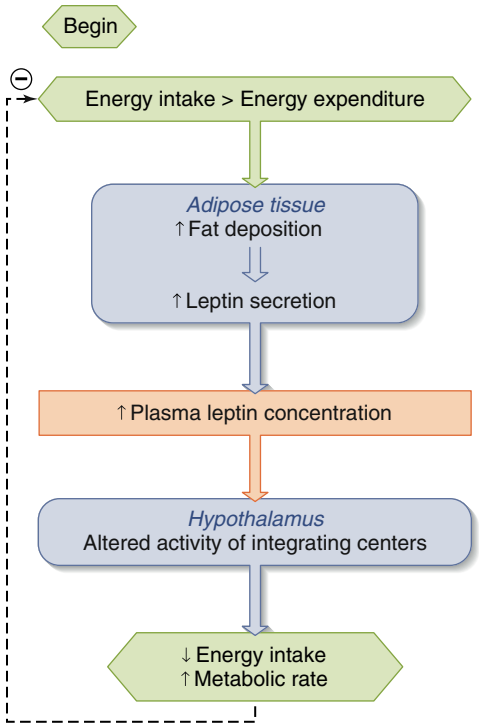


Figure 16.14 Postulated function of leptin in the control of total-body energy stores. Note that the direction of the arrows within the boxes would be reversed if energy (food) intake were less than energy expenditure.

PHYSIOLOGICAL INQUIRY

- Under what circumstances might the appetite-suppressing action of leptin be counterproductive?

Answer can be found at end of chapter.

Although we have focused on leptin and other factors as satiety signals, it is important to realize that a primary function of leptin is to increase metabolic rate. If a person is subjected to starvation, his or her adipocytes begin to shrink, as catabolic hormones mobilize triglycerides from adipocytes. This decrease in size causes a proportional reduction in leptin secretion from the shrinking cells. The decrease in leptin concentration removes the signal that normally inhibits appetite and speeds up metabolism. The result is that a loss of fat mass leads to a decrease in leptin and, thereby, a decrease in BMR and an increase in appetite. This may be the true evolutionary significance of leptin, namely that its decline in the blood results in a decreased BMR, thereby prolonging life during periods of starvation.

In addition to leptin, another recently discovered hormone appears to be an important regulator of appetite. **Ghrelin** (GREH-lin) is a 28-amino-acid polypeptide synthesized and released primarily from enteroendocrine cells in the stomach. Ghrelin is also produced in smaller amounts from other gastrointestinal and non-gastrointestinal tissues.

Ghrelin has several major functions that have been identified in experimental animals and that appear to be true in humans.

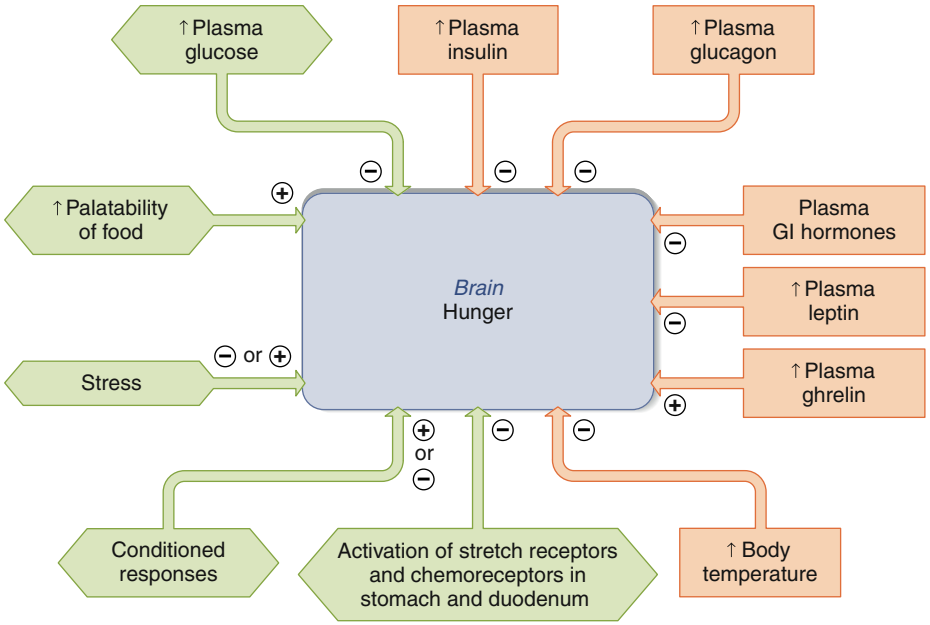


Figure 16.15 Short-term inputs controlling appetite and, consequently, food intake. The ⊖ symbols denote hunger suppression, and the ⊕ symbols denote hunger stimulation.

PHYSIOLOGICAL INQUIRY

- As shown, stretch receptors in the gut after a meal can suppress hunger. Would drinking a large glass of water before a meal be an effective means of dieting?

Answer can be found at end of chapter.

One is to increase *g*rowth *h*ormone *rel*ease—the derivation of the word *ghrelin*—from the anterior pituitary gland. The major function of ghrelin pertinent to this chapter is to increase hunger by stimulating NPY and other neuropeptides in the feeding centers in the hypothalamus. Ghrelin also decreases the breakdown of fat and increases gastric motility and acid production. It makes sense, then, that the major stimuli to ghrelin are fasting and a low-calorie diet.

Ghrelin, therefore, participates in several feedback loops. Fasting or a low-calorie diet leads to an increase in ghrelin. This stimulates hunger and, if food is available, food intake. The food intake subsequently decreases ghrelin, possibly through stomach distention, caloric absorption, or some other mechanism.

Note that glucagon is included in Figure 16.15 as an inhibitor of appetite. Why should this be? Recall that in addition to hypoglycemia, stress (the sympathetic nervous system) also stimulates glucagon secretion. During such times, appetite is generally suppressed and the body relies on stored energy. The evolutionary benefit of this for vertebrates is clear: If a hungry animal must decide between obtaining food or fleeing danger, suppressing appetite removes one of the competing drives.

Overweight and Obesity

The clinical definition of ***overweight*** is a functional one, a state in which an increased amount of fat in the body results in a significant impairment of health from a variety of diseases or disorders—notably, hypertension, atherosclerosis, heart disease, diabetes, and sleep apnea. ***Obesity*** denotes a particularly large accumulation of fat—that is, extreme overweight. The difficulty has been establishing at what point fat accumulation begins to constitute a health risk. This is evaluated by epidemiologic studies that correlate disease rates with some measure of the amount of fat in the body. Currently, a simple method in use for assessing the latter is not the body weight but the **body mass index (BMI),** which is calculated by dividing the weight (in kilograms) by the square of the height (in meters). For example, a 70 kg person with a height of 180 cm would have a BMI of 21.6 kg/m^2 (70/1.8^2).

Current National Institutes of Health guidelines categorize BMIs of greater than 25 kg/m^2 as overweight (i.e., as having some increased health risk because of excess fat) and those greater than 30 kg/m^2 as obese, with a significantly increased health risk. According to these criteria, more than half of U.S. women and men age 20 and older are now considered to be overweight and one-quarter or more to be clinically obese! Even more troubling is that the incidence of childhood overweight and obesity is increasing in the United States and other countries. These guidelines, however, are controversial. First, the epidemiologic studies do not always agree as to where along the continuum of BMIs between 25 and 30 kg/m^2 health risks begin to significantly increase. Second, even granting increased risk above a BMI of 25 kg/m^2, the studies do not always account for confounding factors associated with being overweight or even obese, particularly a sedentary lifestyle. Instead, the increased health risk may be at least partly due to lack of physical activity, not body fat, per se.

To add to the complexity, there is growing evidence that not just total fat but where the fat is located has important consequences. Specifically, people with large amounts of abdominal fat are at greater risk for developing serious conditions such as diabetes and cardiovascular diseases than people whose fat is mainly in the lower body on the buttocks and thighs. There is currently no agreement as to the explanation of this phenomenon, but there are important differences in the physiology of adipose-tissue cells in these regions. For example, adipose-tissue cells in the abdomen are much more adept at breaking down fat stores and releasing the products into the blood.

What is known about the underlying causes of obesity? Identical twins who have been separated soon after birth and raised in

different households manifest strikingly similar body weights and incidences of obesity as adults. Twin studies, therefore, indicate that genetic factors are important in contributing to obesity. It has been postulated that natural selection favored the evolution in our ancestors of so-called **thrifty genes,** which boosted the ability to store fat from each meal in order to sustain people through the next fast. Given today's relative abundance of high-fat foods in many countries, such an adaptation is now a liability. Despite the importance of genetic factors, psychological, cultural, and social factors can also have a significant function. For example, the increasing incidence of obesity in the United States and other industrialized nations during the past 50 years cannot be explained by changes in our genes.

Much recent research has focused on possible abnormalities in the leptin system as a cause of obesity. In one strain of mice (shown in the chapter-opening photo), the gene that codes for leptin is mutated so that adipose-tissue cells produce an abnormal, inactive leptin, resulting in hereditary obesity. The same is *not* true, however, for the vast majority of obese people. The leptin secreted by these people is normal, and leptin concentrations in the blood are increased, not decreased. This observation indicates that leptin secretion is not at fault in these people. Consequently, such people are leptin-resistant in much the same way that people with type 2 diabetes mellitus are insulin-resistant (see the Case Study in Chapter 5 for a discussion of target cell resistance).

The methods and goals of treating obesity are now undergoing extensive rethinking. An increase in body fat must be due to an excess of energy intake over energy expenditure, and low-calorie diets have long been the mainstay of therapy. However, it is now clear that such diets alone have limited effectiveness in obese people; over 90% regain all or most of the lost weight within 5 years. One important reason for the ineffectiveness of such diets is that, as described earlier, the person's metabolic rate decreases as leptin concentration decreases, sometimes decreasing low enough to prevent further weight loss on as little as 1000 calories a day. Because of this, many obese people continue to gain weight or remain in stable energy balance on a caloric intake equal to or less than the amount consumed by people of healthy weight. These persons must either have less physical activity than normal or have lower basal metabolic rates. Finally, many obese individuals who try to diet down to desirable weights suffer medically, physically, and psychologically. This is what would be expected if the body were "trying" to maintain body weight (more specifically, fat stores) at the higher set point.

Such studies, taken together, indicate that crash diets are not an effective long-term method for controlling weight. Instead, caloric intake should be set at a level that can be maintained for the rest of one's life. Such an intake in an overweight person should lead to a slow, steady weight loss of no more than 1 pound per week until the body weight stabilizes at a new, lower level. The most important precept is that any program of weight loss should include increased physical activity. The exercise itself uses calories, but more importantly, it partially offsets the tendency, described earlier, for the metabolic rate to decrease during long-term caloric restriction and weight loss.

Let us calculate how rapidly a person can expect to lose weight on a reducing diet (assuming, for simplicity, no change in energy expenditure). Suppose a person whose steady-state metabolic rate per 24 h is 2000 kcal goes on a 1000 kcal/day diet. How much of the person's own body fat will be required to supply this additional 1000 kcal/day? Because fat contains 9 kcal/g,

$$\frac{1000 \text{ kcal/day}}{9 \text{ kcal/g}} = 111 \text{ g/day, or } 777 \text{ g/week}$$

Approximately another 77 g of water is lost from the adipose tissue along with this fat (adipose tissue is 10% water), so that the grand total for 1 week's loss equals 854 g, or 1.8 pounds. Therefore, even on this severe diet, the person can reasonably expect to lose approximately this amount of weight per week, assuming no decrease in metabolic rate occurs.

Eating Disorders: Anorexia Nervosa and Bulimia Nervosa

Two of the major eating disorders are found primarily in adolescent girls and young women. The typical person with ***anorexia nervosa*** becomes pathologically obsessed with her weight and body image. She may decrease her food intake so severely that she may die of starvation. There are many other abnormalities associated with anorexia nervosa—cessation of menstrual periods, low blood pressure, low body temperature, hypoglycemia, and altered blood concentrations of many hormones, including ghrelin. It is likely that these are simply the results of starvation, although it is possible that some represent signs, along with the eating disturbances, of primary hypothalamic malfunction.

Bulimia nervosa, usually called simply *bulimia,* is a disorder characterized by recurrent episodes of binge eating. It is usually associated with regular self-induced vomiting and use of laxatives or diuretics, as well as strict dieting, fasting, or vigorous exercise to lose weight or to prevent weight gain. Like individuals with anorexia nervosa, those with bulimia manifest a persistent heightened concern with body weight, although they generally remain within 10% of their ideal weight. This disorder, too, is accompanied by a variety of physiological abnormalities, but it is unknown in some cases whether they are causal or secondary.

In addition to anorexia and bulimia, rare lesions or tumors within the hypothalamic centers that normally regulate appetite can result in overfeeding or underfeeding.

What Should We Eat?

In recent years, more and more dietary factors have been associated with the cause or prevention of many diseases or disorders, including not only coronary artery disease but hypertension, cancer, birth defects, osteoporosis, and others. These associations come mainly from animal studies, epidemiologic studies on people, and basic research concerning potential mechanisms. Some of these findings may be difficult to interpret or may be conflicting. One of the most commonly used sets of dietary recommendations, issued by the National Research Council, is presented in **Table 16.6**.

16.6 Regulation of Body Temperature

In the preceding discussion, it was emphasized that energy expenditure is linked to our ability to maintain a stable, homeostatic body temperature. Heat is a by-product of many chemical reactions,

TABLE 16.6 Summary of National Research Council Dietary Recommendations

Reduce fat intake to 30% or less of total calories; most fat consumed should be mono- or polyunsaturated fats. Reduce saturated fatty acid intake to less than 10% of calories and intake of cholesterol to less than 300 mg daily.
Every day eat five or more servings of a combination of vegetables and fruits, especially green and yellow vegetables and citrus fruits. Also, increase complex carbohydrates by eating six or more daily servings of a combination of whole-grain breads, cereals, and legumes.
Maintain protein intake at moderate levels (approximately 0.8 g/kg body mass).
Balance food intake and physical activity to maintain appropriate body weight.
Alcohol consumption is not recommended. For those who drink alcoholic beverages, limit consumption to the equivalent of 1 ounce of pure alcohol in a single day.
Limit total daily intake of sodium to 2.3 g or less.
Maintain adequate calcium intake.
Avoid taking dietary supplements in excess of the RDA (Recommended Dietary Allowance) in any one day.
Maintain an optimal intake of fluoride, particularly during the years of primary and secondary tooth formation and growth. Most bottled water does not contain fluoride.

including those involved in the breakdown of organic nutrients for energy. The body's chemical reactions, in turn, are typically accelerated at higher temperatures. Thus, energy consumption, energy expenditure, and heat production or loss are all interlinked. In this section, we discuss the mechanisms by which the body gains or loses heat in a variety of healthy or pathological settings.

Humans are **endotherms,** meaning that they generate their own internal body heat and do not rely on the energy of sunlight to warm the body. Moreover, humans maintain their body temperatures within very narrow limits despite wide fluctuations in ambient temperature and are, therefore, also known as **homeotherms.** The relatively stable body temperature frees biochemical reactions from fluctuating with the external temperature. However, the maintenance of a warm body temperature (approximately 37°C in healthy persons) imposes a requirement for precise regulatory mechanisms because large elevations of temperature cause nerve malfunction and protein denaturation. Some people suffer convulsions at a body temperature of 41°C (106°F), and 43°C is considered to be the limit for survival.

A few important generalizations about normal human body temperature should be stressed at the outset. (1) Oral temperature averages about 0.5°C less than rectal, which is generally used as an estimate of internal temperature (also known as **core body temperature**). Not all regions of the body, therefore, have the same temperature. (2) Internal temperature is not constant; although it does not vary much, it does change slightly in response to activity patterns and changes in external temperature. Moreover, there is a characteristic circadian fluctuation of about 1°C (**Figure 16.16**), with temperature being lowest during the night and highest during the day. (3) An added variation in women is a higher temperature during the second half of the menstrual cycle due to the effects of the hormone progesterone.

Temperature regulation can be studied by our usual balance methods. The total heat content gained or lost by the body is determined by the net difference between heat gain (from the environment and produced in the body) and heat loss. Maintaining a stable body temperature means that, in the steady state, heat gain must equal heat loss.

Mechanisms of Heat Loss or Gain

The surface of the body can lose heat to the external environment by radiation, conduction, convection, and the evaporation of water (**Figure 16.17**). Before defining each of these processes, however, it must be emphasized that radiation, conduction, and convection can, under certain circumstances, lead to heat *gain* instead of loss.

Radiation is the process by which the surfaces of all objects constantly emit heat in the form of electromagnetic waves. It is a principle of physics that the rate of heat emission is determined by the temperature of the radiating surface. As a result, if the body surface is warmer than the various surfaces in the environment, net heat is lost from the body, the rate being directly dependent upon the temperature difference between the surfaces. Conversely, the body gains heat by absorbing electromagnetic energy radiated by the sun.

Conduction is the loss or gain of heat by transfer of thermal energy during collisions between adjacent molecules. In essence, heat is "conducted" from molecule to molecule. The body surface loses or gains heat by conduction through direct contact with cooler or warmer substances, including the air or water. Not all substances, however, conduct heat equally. Water is a better conductor of heat than is air; therefore, more heat is lost from the body in water than in air of similar temperature.

Convection is the process whereby conductive heat loss or gain is aided by movement of the air or water next to the body. For

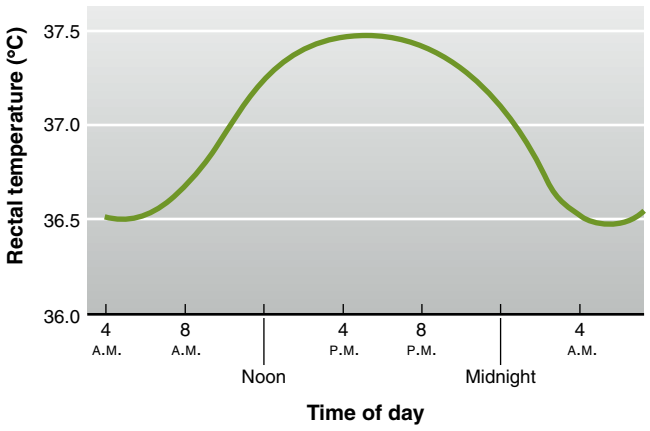


Figure 16.16 Circadian changes in core (measured as rectal) body temperature in a typical person. This figure does not take into account daily minor swings in temperature due to such things as exercise and eating; nor are the absolute values on the *y*-axis representative of all individuals. Source: Adapted from Scales, W. E., A. J. Vander, M. B. Brown, and J. J. Kluger: *American Journal of Physiology*, **65**:1840 (1988).

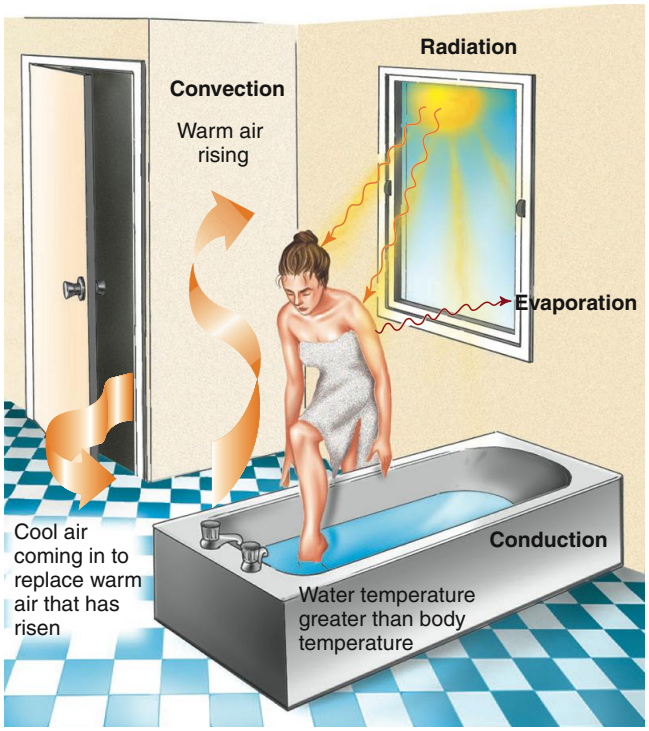


Figure 16.17 Mechanisms of heat transfer.

PHYSIOLOGICAL INQUIRY

- Evaporation is an important mechanism for eliminating heat, particularly on a hot day or when exercising. What are some of the negative consequences of this mechanism of heat loss?

Answer can be found at end of chapter.

example, air next to the body is heated by conduction. Because warm air is less dense than cool air, the cool air sinks and forces the heated air to rise. This carries away the heat just taken from the body. The air that moves away is replaced by cooler air, which in turn follows the same pattern. Convection is always occurring because warm air is less dense and therefore rises, but it can be greatly facilitated by external forces such as wind or fans. Consequently, convection aids conductive heat exchange by continuously maintaining a supply of cool air. Therefore, in the rest of this chapter, the term *conduction* will also imply convection.

Evaporation of water from the skin and membranes lining the respiratory tract is the other major process causing loss of body heat. A very large amount of energy—600 kcal/L—is required to transform water from the liquid to the gaseous state. As a result, whenever water vaporizes from the body's surface, the heat required to drive the process is conducted from the surface, thereby cooling it.

Temperature-Regulating Reflexes

Temperature regulation offers a classic example of a homeostatic control system, as described in Chapter 1 (see Figure 1.8). The balance between heat production (gain) and heat loss is continuously being disturbed, either by changes in metabolic rate (exercise being the most powerful influence) or by changes in the external environment such as air temperature. The resulting changes in body temperature are detected by thermoreceptors (see Chapter 7). These receptors initiate reflexes that change the output of various effectors so that heat production and/or loss are modified and body temperature is restored toward normal.

Figure 16.18 summarizes the components of these reflexes. There are two locations of thermoreceptors, one in the skin (**peripheral thermoreceptors**) and the other (**central thermoreceptors**) in deep body structures, including abdominal organs and thermoreceptive neurons in the hypothalamus. Because it is the core body temperature—not the skin temperature—that is maintained in a narrow homeostatic range, the central thermoreceptors provide the essential negative feedback component of the reflexes. The peripheral thermoreceptors provide feedforward information, as described in Chapter 1, and also account for the ability to identify a hot or cold area of the skin.

The hypothalamus serves as the primary overall integrator of the reflexes, but other brain centers also exert some control over specific components of the reflexes. Output from the hypothalamus and the other brain areas to the effectors is via (1) sympathetic nerves to the sweat glands, skin arterioles, and the adrenal medulla; and (2) motor neurons to the skeletal muscles.

Control of Heat Production

Changes in muscle activity constitute the major control of heat production for temperature regulation. The first muscle change in response to a decrease in core body temperature is a gradual and general increase in skeletal muscle contraction. This may lead to shivering, which consists of oscillating, rhythmic muscle contractions and relaxations occurring at a rapid rate. During shivering, the efferent motor nerves to the skeletal muscles are influenced by descending pathways under the primary control of the hypothalamus. Because almost no external work is performed by shivering, most of the energy liberated by the metabolic machinery appears as internal heat, a process known as **shivering thermogenesis.** People also use their muscles for voluntary heat-producing activities such as foot stamping and hand rubbing.

The opposite muscle reactions occur in response to heat. Basal muscle contraction is reflexively decreased, and voluntary movement is also diminished. These attempts to decrease heat production are limited, however, because basal muscle contraction is quite low to start with and because any increased core temperature produced by the heat acts *directly* on cells to increase metabolic rate. In other words, an increase in cellular temperature directly accelerates the rate at which all of its chemical reactions occur. This is due to the increased thermal motion of dissolved molecules, making it more likely that they will encounter each other. The result is that ATP is expended at a higher rate because ATP participates in many of a cell's chemical reactions. This, in turn, results in a compensatory increase in ATP production from cellular energy stores, which also generates heat as a by-product of metabolism. Thus, increasing cellular temperature can itself result in the production of additional heat through increased metabolism.

Muscle contraction is not the only process controlled in temperature-regulating reflexes. In many experimental mammals, chronic cold exposure induces an increase in metabolic rate (and therefore heat production) that is not due to increased muscle activity and is termed **nonshivering thermogenesis.**

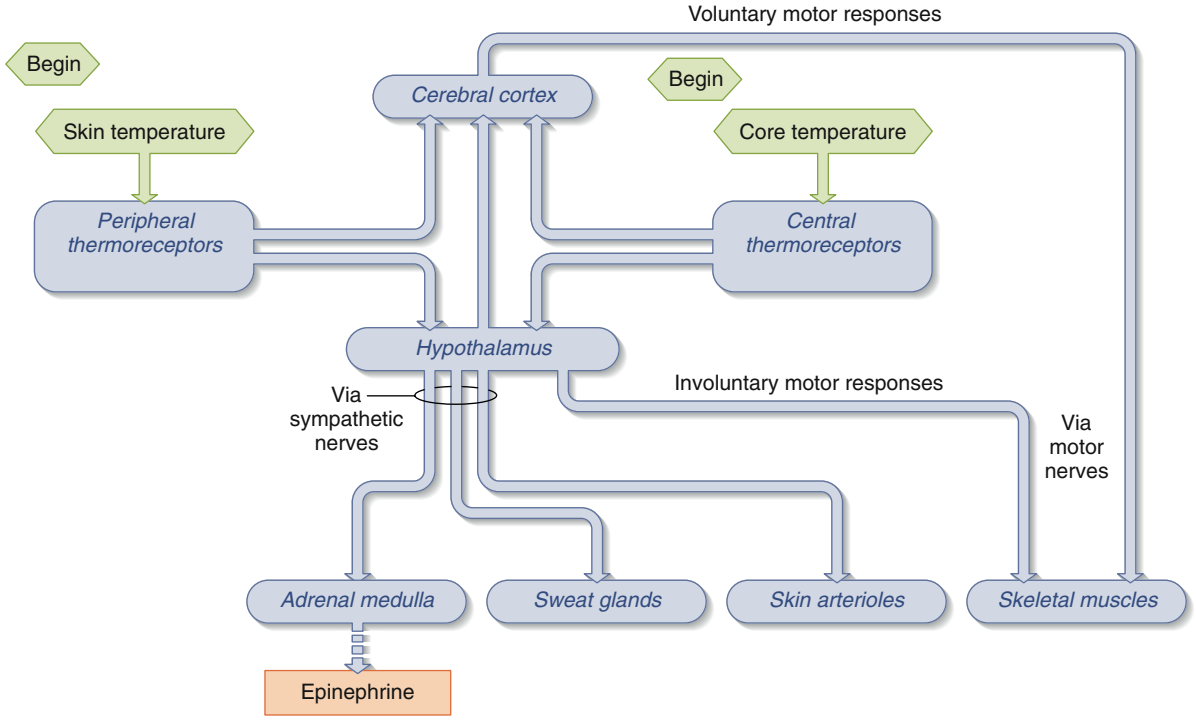


Figure 16.18 Summary of temperature-regulating mechanisms beginning with peripheral thermoreceptors and central thermoreceptors. The dashed arrow from the adrenal medulla indicates that this hormonal pathway is of minor importance in adult human beings. The solid arrows denote neural pathways. The hypothalamus influences sympathetic nerves via descending pathways.

Its causes include an increase in the activity of a special type of adipose tissue called brown fat, or **brown adipose tissue.** This type of adipose tissue is stimulated by thyroid hormone, epinephrine, and the sympathetic nervous system; it contains large amounts of a class of proteins called uncoupling proteins. These proteins uncouple oxidation from phosphorylation (Chapter 3) and, in effect, make metabolism less efficient (less ATP is generated). The major product of this inefficient metabolism is heat, which then contributes to maintaining body temperature. Brown adipose tissue is present in infant humans (and to a smaller extent in adults). Nonshivering thermogenesis does occur in infants, therefore, whose shivering mechanism is not yet fully developed.

Control of Heat Loss by Radiation and Conduction

For purposes of temperature control, the body may be thought of as a central core surrounded by a shell consisting of skin and subcutaneous tissue. The temperature of the central core is regulated at approximately 37°C, but the temperature of the outer surface of the skin changes considerably.

If the skin and its underlying tissue were a perfect insulator, minimal heat would be lost from the core. The temperature of the outer skin surface would equal the environmental temperature, and net conduction would be zero. The skin is not a perfect insulator, however, so the temperature of its outer surface generally is somewhere between that of the external environment and that of the core. Instead of acting as an insulator, the skin functions as a regulator of heat exchange. Its effectiveness in this capacity is subject to physiological control by a change in blood flow. The more blood reaching the skin from the core, the more closely the skin's temperature approaches that of the core. In effect, the blood vessels can carry heat to the skin surface to be lost to the external environment. These vessels are controlled largely by vasoconstrictor sympathetic nerves, which are reflexively stimulated in response to cold and inhibited in response to heat. There is also a population of sympathetic neurons to the skin whose neurotransmitters cause active vasodilation. Certain areas of skin participate much more than others in all these vasomotor responses, and so skin temperatures vary with location.

Finally, the three *behavioral* mechanisms for altering heat loss by radiation and conduction are changes in surface area, changes in clothing, and choice of surroundings. Curling up into a ball, hunching the shoulders, and similar maneuvers in response to cold reduce the surface area exposed to the environment, thereby decreasing heat loss by radiation and conduction. In human beings, clothing is also an important component of temperature regulation, substituting for the insulating effects of feathers in birds and fur in other mammals. The outer surface of the clothes forms the true "exterior" of the body surface. The skin loses heat directly to the air space trapped by the clothes, which in turn pick up heat from the inner air layer and transfer it to the external environment. The insulating ability of clothing is determined primarily by the thickness of the trapped air layer. A third familiar behavioral mechanism for altering heat loss is to seek out warmer or colder surroundings, for example, by moving from a shady spot into the sunlight.

Control of Heat Loss by Evaporation

Even in the absence of sweating, there is loss of water by diffusion through the skin, which is not completely waterproof. A similar amount is lost from the respiratory lining during expiration. These

two losses are known as **insensible water loss** and amount to approximately 600 mL/day in human beings. Evaporation of this water can account for a significant fraction of total heat loss. In contrast to this passive water loss, sweating requires the active secretion of fluid by **sweat glands** and its extrusion into ducts that carry it to the skin surface.

Production of sweat is stimulated by sympathetic nerves to the glands. Sweat is a dilute solution containing sodium chloride as its major solute. Sweating rates of over 4 L/h have been reported; the evaporation of 4 L of water would eliminate almost 2400 kcal of heat from the body!

Sweat must evaporate in order to exert its cooling effect. The most important factor determining evaporation rate is the water vapor concentration of the air—that is, the relative humidity. The discomfort suffered on humid days is due to the failure of evaporation; the sweat glands continue to secrete, but the sweat simply remains on the skin or drips off.

Integration of Effector Mechanisms By altering heat loss, changes in skin blood flow alone can regulate body temperature over a range of environmental temperatures known as the **thermoneutral zone.** In humans, the thermoneutral zone is approximately 25°C to 30°C or 75°F to 86°F for a nude individual. At temperatures lower than this, even maximal vasoconstriction of blood vessels in the skin cannot prevent heat loss from exceeding heat gain and the body must increase its heat production to maintain temperature. At environmental temperatures above the thermoneutral zone, even maximal vasodilation cannot eliminate heat as fast as it is produced, and another heat-loss mechanism—sweating—therefore comes strongly into play. At environmental temperatures above that of the body, heat is actually added to the body by radiation and conduction. Under such conditions, evaporation is the sole mechanism for heat loss. A person's ability to tolerate such temperatures is determined by the humidity and by his or her maximal sweating rate. For example, when the air is completely dry, a hydrated person can tolerate an environmental temperature of 130°C (225°F) for 20 min or longer, whereas very humid air at 46°C (115°F) is bearable for only a few minutes.

Temperature Acclimatization

Changes in the onset, volume, and composition of sweat determine the ability to adapt to chronic high temperatures. A person newly arrived in a hot environment has poor ability to do work; body temperature increases, and severe weakness may occur. After several days, there is a great improvement in work tolerance, with much less increase in body temperature, and the person is said to have acclimatized to the heat. Body temperature does not increase as much because sweating begins sooner and the volume of sweat produced is greater.

There is also an important change in the composition of the sweat, namely, a significant reduction in its ion concentration. This adaptation, which minimizes the loss of Na^+ from the body via sweat, is due to increased secretion of the adrenal cortex hormone aldosterone. The sweat-gland secretory cells produce a solution with a Na^+ concentration similar to that of plasma, but some of the sodium ions are absorbed back into the blood as the secretion flows along the sweat-gland ducts toward the skin surface. Aldosterone stimulates this absorption in a manner identical to its stimulation of Na^+ reabsorption in the renal tubules.

Cold acclimatization has been much less studied than heat acclimatization because of the difficulty of subjecting people to total-body cold stress over long enough periods to produce acclimatization. Moreover, people who live in cold climates generally dress very warmly and so would not develop acclimatization to the cold.

16.7 Fever and Hyperthermia

Fever is an increase in core body temperature due to a resetting of the "thermostat" in the hypothalamus. A person with a fever still regulates body temperature in response to heat or cold but at a higher set point. The most common cause of fever is infection, but physical trauma and tissue damage can also induce fever.

The onset of fever during infection is often gradual, but it is most striking when it occurs rapidly in the form of a chill. In such cases, the temperature set point of the hypothalamic thermostat is suddenly increased. Because of this, the person feels cold, even though his or her actual body temperature may be normal. As a result, the typical actions that are used to increase body temperature, such as vasoconstriction and shivering, occur. The person may also curl up and put on blankets. This combination of decreased heat loss and increased heat production serves to drive body temperature up to the new set point, where it stabilizes. It will continue to be regulated at this new value until the thermostat is reset to normal and the fever "breaks." The person then feels hot, throws off the covers, and manifests profound vasodilation and sweating.

What is the basis for the thermostat resetting? Chemical messengers collectively termed **endogenous pyrogen** (**EP**) are released from macrophages (as well as other cell types) in the presence of infection or other fever-producing stimuli. The next steps vary depending on the precise stimulus for the release of EP. As illustrated in **Figure 16.19**, in some cases, EP probably circulates in the blood to act upon the thermoreceptors in the hypothalamus (and perhaps other brain areas), altering their input to the integrating centers. In other cases, EP may be produced by macrophage-like cells in the liver and stimulate neural receptors there that give rise to afferent neural input to the hypothalamic thermoreceptors. In both cases, the immediate cause of the resetting is a local synthesis and release of prostaglandins within the hypothalamus. ***Aspirin*** reduces fever by inhibiting this prostaglandin synthesis.

The term *EP* was coined at a time when the identity of the chemical messenger(s) was not known. At least three proteins—interleukin 1-beta (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNFα)—are now known to function as EPs. In addition to their effects on temperature, these proteins have many other effects (described in Chapter 18) that enhance resistance to infection and promote the healing of damaged tissue.

One would expect fever, which is such a consistent feature of infection, to have some important protective function. Most evidence suggests that this is the case. For example, increased body temperature stimulates a large number of the body's defensive responses to infection, including the proliferation and activity of pathogen-fighting white blood cells. The likelihood that fever is a beneficial response raises important questions about the use of

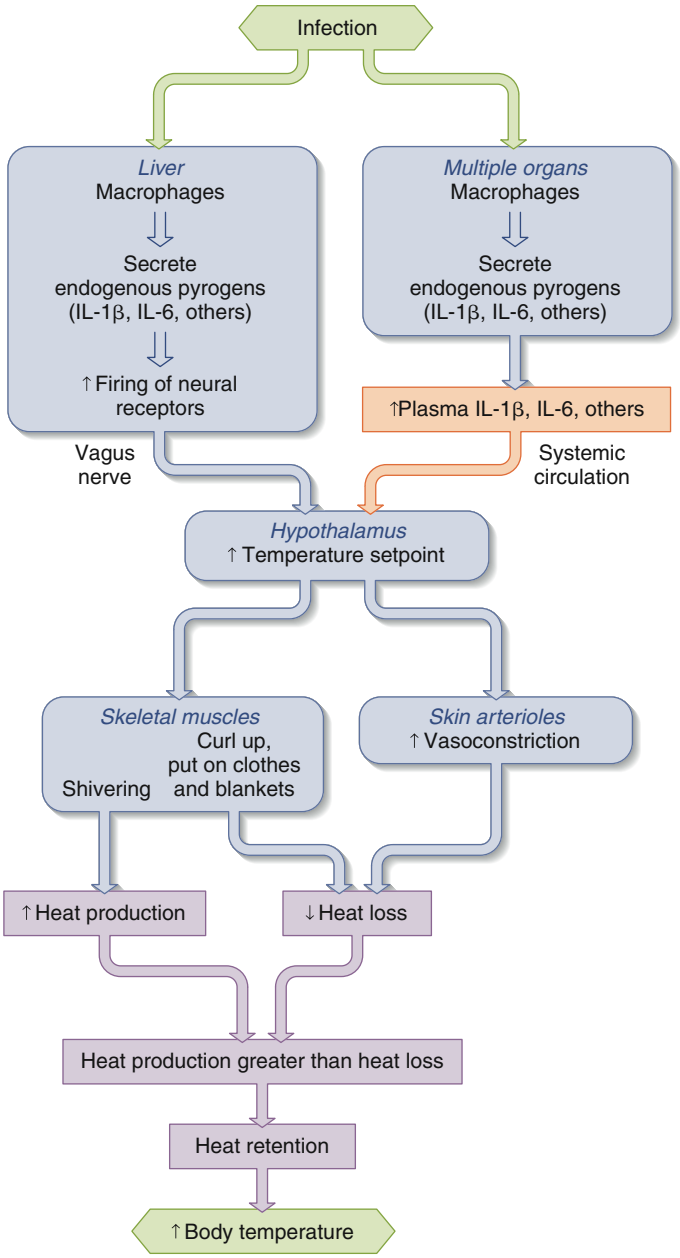


Figure 16.19 Pathway by which infection causes fever (IL - 1β = Interleukin 1β; IL - 6 = Interleukin 6). The effector responses serve to *increase* body temperature during an infection.

PHYSIOLOGICAL INQUIRY

- Which organ systems contribute to the fever-induced increase in body temperature, thereby illustrating the general principle of physiology that the functions of organ systems are coordinated with each other?

Answer can be found at end of chapter.

aspirin and other drugs to suppress fever during infection. It must be emphasized that these questions apply to the usual modest fevers. There is no question that an extremely high fever can be harmful—particularly in its effects on the central nervous system—and must be vigorously opposed with drugs and other forms of therapy.

Fever, then, is an increased body temperature caused by an elevation of the thermal set point. When body temperature is increased for any other reason beyond a narrow normal range but without a change in the temperature set point, it is termed ***hyperthermia.*** The most common cause of hyperthermia in a typical person is exercise; the increase in body temperature above set point is due to the internal heat generated by the exercising muscles.

As shown in **Figure 16.20**, heat production increases immediately during the initial stage of exercise and exceeds heat loss, causing heat storage in the body and an increase in the core temperature. This increase in core temperature triggers reflexes, via the central thermoreceptors, that cause increased heat loss. As skin blood flow and sweating increase, the discrepancy between heat production and heat loss starts to diminish but does not disappear. Therefore, core temperature continues to increase. Ultimately, core temperature will be high enough to drive (via the central thermoreceptors) the heat-loss reflexes at a rate such that heat loss once again equals heat production. At this point, core temperature stabilizes at this elevated value despite continued exercise. In some situations, hyperthermia may lead to life-threatening consequences.

Heat exhaustion is a state of collapse, often taking the form of fainting, due to hypotension brought on by depletion of plasma volume secondary to sweating and extreme dilation of skin blood vessels. Recall from Chapter 12 that blood pressure, cardiac output, and total peripheral resistance are related according to the equation $MAP = CO \times TPR$. Thus, decreases in both cardiac output (due to the decreased plasma volume) and peripheral resistance (due to the vasodilation) contribute to the hypotension. Heat exhaustion occurs as a direct consequence of the activity of heat-loss mechanisms. Because these mechanisms have been so active, the body temperature is only modestly elevated. In a sense, heat exhaustion is a safety valve that, by forcing a cessation of work in a hot environment

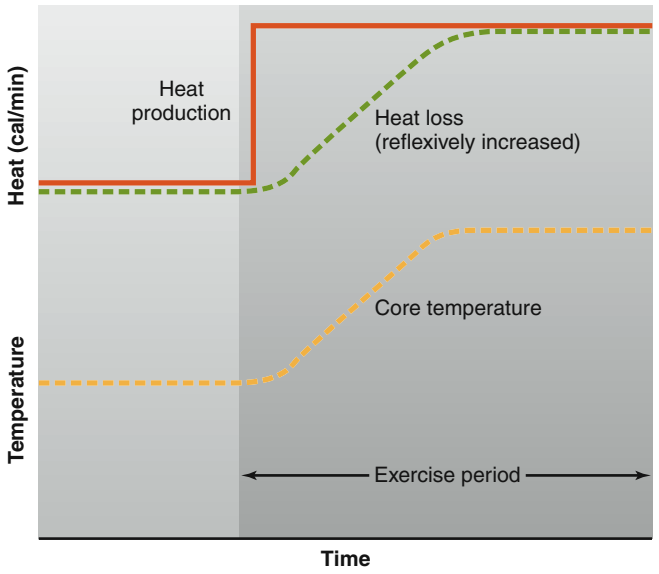


Figure 16.20 Thermal changes during exercise. Heat loss is reflexively increased. When heat loss once again equals heat production, core temperature stabilizes.

when heat-loss mechanisms are overtaxed, prevents the larger increase in body temperature that would cause the far more serious condition of heatstroke.

In contrast to heat exhaustion, ***heatstroke*** represents a complete breakdown in heat-regulating systems so that body temperature keeps increasing. It is an extremely dangerous situation characterized by collapse, delirium, seizures, or prolonged unconsciousness—all due to greatly increased body temperature. It almost always occurs in association with exposure to or overexertion in hot and humid environments. In some individuals, particularly elderly persons, heatstroke may appear with no apparent prior period of severe sweating (refer back to the Chapter 1 Clinical Case Study for an example), but in most cases, it comes on as the end stage of prolonged untreated heat exhaustion. Exactly what triggers the transition to heatstroke is not clear, although impaired circulation to the brain due to dehydration is one factor. The striking finding, however, is that even in the face of a rapidly increasing body temperature, the person fails to sweat. Heatstroke is a harmful positive feedback situation in which the increasing body temperature directly stimulates metabolism, that is, heat production, which further increases body temperature. For both heat exhaustion and heatstroke, the remedy is external cooling, fluid replacement, and cessation of activity. ■

SECTION B SUMMARY

General Principles of Energy Expenditure

I. The energy liberated during a chemical reaction appears either as heat or work.
II. Total energy expenditure = Heat produced + External work done + Energy stored
III. Metabolic rate is influenced by the many factors summarized in Table 16.5.
IV. Metabolic rate is increased by the thyroid hormones and epinephrine.

Regulation of Total-Body Energy Stores

I. Energy storage as fat can be positive when the metabolic rate is less than, or negative when the metabolic rate is greater than, the energy content of ingested food.
   a. Energy storage is regulated mainly by reflexive adjustment of food intake.
   b. In addition, the metabolic rate increases or decreases to some extent when food intake is chronically increased or decreased, respectively.
II. Food intake is controlled by leptin, which is secreted by adipose-tissue cells, and a variety of satiety factors, as summarized in Figures 16.14 and 16.15.
III. Being overweight or obese, the result of an imbalance between food intake and metabolic rate, increases the risk of many diseases.

Regulation of Body Temperature

I. Core body temperature shows a circadian rhythm, with temperature highest during the day and lowest at night.
II. The body exchanges heat with the external environment by radiation, conduction, convection, and evaporation of water from the body surface.
III. The hypothalamus and other brain areas contain the integrating centers for temperature-regulating reflexes, and both peripheral and central thermoreceptors participate in these reflexes.
IV. Body temperature is regulated by altering heat production and/or heat loss so as to change total-body heat content.
   a. Heat production is altered by increasing muscle tone, shivering, and voluntary activity.
   b. Heat loss by radiation, conduction, and convection depends on the temperature difference between the skin surface and the environment.
   c. In response to cold, skin temperature is decreased by decreasing skin blood flow through reflexive stimulation of the sympathetic nerves to the skin. In response to heat, skin temperature is increased by inhibiting these nerves.
   d. Behavioral responses, such as putting on more clothes, also influence heat loss.
   e. Evaporation of water occurs all the time as insensible loss from the skin and respiratory lining. Additional water for evaporation is supplied by sweat, stimulated by the sympathetic nerves to the sweat glands.
   f. Increased heat production is essential for temperature regulation at environmental temperatures below the thermoneutral zone, and sweating is essential at temperatures above this zone.
V. Temperature acclimatization to heat is achieved by an earlier onset of sweating, an increased volume of sweat, and a decreased salt concentration of the sweat.

Fever and Hyperthermia

I. Fever is due to a resetting of the temperature set point so that heat production is increased and heat loss is decreased in order to increase body temperature to the new set point and keep it there. The stimulus is endogenous pyrogen, in the form of interleukin 1 and other proteins.
II. The hyperthermia of exercise is due to the increased heat produced by the muscles, and it is partially offset by skin vasodilation.
III. Extreme increases in body temperature can result in heat exhaustion or heatstroke. In heat exhaustion, blood pressure decreases due to vasodilation. In heatstroke, the normal thermoregulatory mechanisms fail; thus, heatstroke can be fatal.

SECTION B REVIEW QUESTIONS

1. State the formula relating total energy expenditure, heat produced, external work, and energy storage.
2. What two hormones alter the basal metabolic rate?
3. State the equation for total-body energy balance. Describe the three possible states of balance with regard to energy storage.
4. What happens to the basal metabolic rate after a person has either lost or gained weight?
5. List several satiety signals; where do satiety signals act?
6. List three beneficial effects of exercise in a weight-loss program.
7. Compare and contrast the four mechanisms for heat loss.
8. Describe the control of skin blood vessels during exposure to cold or heat.
9. With a diagram, summarize the reflexive responses to heat or cold. What are the dominant mechanisms for temperature regulation in the thermoneutral zone and in temperatures below and above this range?
10. What changes are exhibited by a heat-acclimatized person?
11. Summarize the sequence of events leading to a fever; contrast this to the sequence leading to hyperthermia during exercise.

SECTION B KEY TERMS

16.4 General Principles of Energy Expenditure

basal metabolic rate (BMR)
calorie
calorigenic effect
diet-induced thermogenesis
external work
internal work

kilocalorie (kcal)
metabolic rate
total energy expenditure

16.5 Regulation of Total-Body Energy Stores

body mass index (BMI)
ghrelin
leptin
neuropeptide Y
thrifty genes

16.6 Regulation of Body Temperature

brown adipose tissue
central thermoreceptors
conduction
convection
core body temperature
endotherms
evaporation
homeotherms
insensible water loss
nonshivering thermogenesis
peripheral thermoreceptors
radiation
shivering thermogenesis
sweat glands
thermoneutral zone

16.7 Fever and Hyperthermia

endogenous pyrogen (EP)

SECTION B CLINICAL TERMS

16.5 Regulation of Total-Body Energy Stores

anorexia nervosa
bulimia nervosa
obesity
overweight

16.7 Fever and Hyperthermia

aspirin
fever
heat exhaustion
heatstroke
hyperthermia

CHAPTER 16

Clinical Case Study: An Overweight Man with Tingling, Thirst, and Blurred Vision

A 46-year-old man visited an ophthalmologist because of recent episodes of blurry vision. In addition to examining the man's eyes, the ophthalmologist took a medical history and assessed the patient's overall health. The patient was 6 feet tall and weighed 265 pounds (BMI equal to 36 kg/m^2). He had recently been experiencing "tingling" sensations in his hands and feet and was sleeping poorly because he was waking up several times during the night with a full bladder. He had also taken to carrying bottled water with him wherever he went, because he often felt very thirsty. He reported that he worked as a taxicab driver and rarely if ever had occasion to engage in much physical activity or exercise. The patient attributed the tingling sensations to "sitting in one position all day" and was convinced that his eye problems were the natural result of aging. Examination of the eyes, however, revealed a greatly weakened accommodation reflex in both eyes (see Chapter 7). These signs and symptoms suggested to the ophthalmologist that the patient might have ***diabetes mellitus,*** and he therefore referred the patient to a physician at the diabetes unit of his local hospital.

Reflect and Review #1

- What are the major functions of insulin, particularly with respect to its effects on plasma glucose?

The physician at the hospital performed a series of tests to confirm the diagnosis of diabetes mellitus. First, the fasting plasma glucose concentration was determined on two separate days. After an overnight fast, blood was drawn and the concentration of glucose in the plasma was determined. Normal values are generally below 100 mg/dL, but the two values determined for this patient were 156 and 144 mg/dL. Consequently, a second test was performed to determine what percentage of the patient's hemoglobin was glycated. It is not uncommon for some proteins in the body to occasionally become bound to glucose (this is not the same process as glycosylation, which is a normal, enzymatically catalyzed reaction that forms a glycoprotein). Such binding is typically permanent and often renders the protein nonfunctional. At any given time, a small percentage of the blood's hemoglobin proteins are bound to glucose. However, the longer the duration of an elevation in plasma glucose, the greater the percentage of glucose-bound hemoglobin, abbreviated HbA1c. Hemoglobin is found in red blood cells, which have a lifetime of 2 to 4 months. Therefore, this test is a measure of the average glucose values in the blood over the previous few months. Normal values are between 4% and 6%, but in our patient, HbA1c was 6.9%. Together, these tests confirmed the diagnosis of diabetes mellitus.

Diabetes mellitus can be due to a deficiency of insulin and/or to a decreased responsiveness to insulin. Diabetes mellitus is therefore classified into two distinct diseases depending on the cause. In ***type 1 diabetes mellitus*** (***T1DM***), formerly called *insulin-dependent diabetes mellitus* or *juvenile diabetes,* insulin is completely or almost completely absent from the islets of Langerhans and the plasma. Therefore, therapy with insulin is essential. In ***type 2 diabetes mellitus*** (***T2DM***), formerly called *non-insulin-dependent diabetes mellitus* or *adult-onset diabetes mellitus,* insulin is present in plasma but cellular sensitivity to insulin is less than normal (in other words, the target cells demonstrate ***insulin resistance***). In many patients with T2DM, the response of the pancreatic beta cells to glucose is also impaired. Therefore, therapy may involve some combination of drugs that increase cellular sensitivity to insulin, increase insulin secretion from beta cells, or decrease hepatic glucose production; or the therapy may involve insulin administration itself.

T1DM is less common, affecting approximately 5% of diabetic patients in the United States. T1DM is due to the total or near-total autoimmune destruction of the pancreatic beta cells by the body's white blood cells. As you will learn in Chapter 18, an autoimmune disease is one in which the body's immune cells attack and destroy normal, healthy tissue. The triggering events for this autoimmune response are not yet fully established. Treatment of T1DM involves the administration of insulin by injection, because insulin administered orally would be destroyed by gastrointestinal acid and enzymes.

Because of insulin deficiency, *untreated* patients with T1DM always have increased glucose concentrations in their blood. The increase in plasma glucose occurs because (1) glucose fails to enter insulin's target cells normally, and (2) the liver continuously makes glucose by glycogenolysis and gluconeogenesis and secretes the glucose into the blood. Recall also that insulin normally suppresses lipolysis and ketone formation. Consequently, another result of the insulin deficiency is pronounced lipolysis with subsequent elevation of plasma glycerol and fatty acids. Many of the fatty acids are then converted by the liver into ketones, which are released into the blood.

If extreme, these metabolic changes culminate in the acute life-threatening emergency called ***diabetic ketoacidosis*** (**Figure 16.21**). Some of the problems are due to the effects that extremely elevated plasma glucose concentration produces on renal function. Chapter 14 pointed out that a typical person does not excrete glucose because all glucose filtered at the renal glomeruli is reabsorbed by the tubules. However, the increased plasma glucose of diabetes mellitus increases the filtered load of glucose beyond the maximum tubular reabsorptive capacity and, therefore, large amounts of glucose are excreted. For the same reasons, large amounts of ketones may also appear in the urine. These urinary losses deplete the body of nutrients and lead to weight loss. Far worse, however, is the fact that these unreabsorbed solutes cause an osmotic diuresis—increased urinary excretion of Na^+ and water, which can lead, by the sequence of events shown in Figure 16.21, to hypotension, brain damage, and death. It should be noted, however, that apart from this extreme example, diabetics are more often prone to hypertension, not hypotension (due to several causes, including vascular and kidney damage).

The other serious abnormality in diabetic ketoacidosis is the increased plasma H^+ concentration caused by the accumulation of ketones. As described in Chapter 3, ketones are four-carbon breakdown products of fatty acids. Two ketones, known as hydroxybutyric acid and acetoacetic acid, are acidic at the pH of blood. This increased H^+ concentration causes brain dysfunction that can contribute to coma and death.

Diabetic ketoacidosis occurs primarily in patients with *untreated* T1DM, that is, those with almost total inability to secrete insulin. However, more than 90% of diabetic patients are in the T2DM category and usually do not develop metabolic derangements severe enough to result in diabetic ketoacidosis. T2DM is a syndrome mainly of overweight adults, typically starting in middle life. However, T2DM is *not* an age-dependent syndrome. As the incidence of childhood obesity has soared in the United States, so too has the incidence of T2DM in children and adolescents. Given

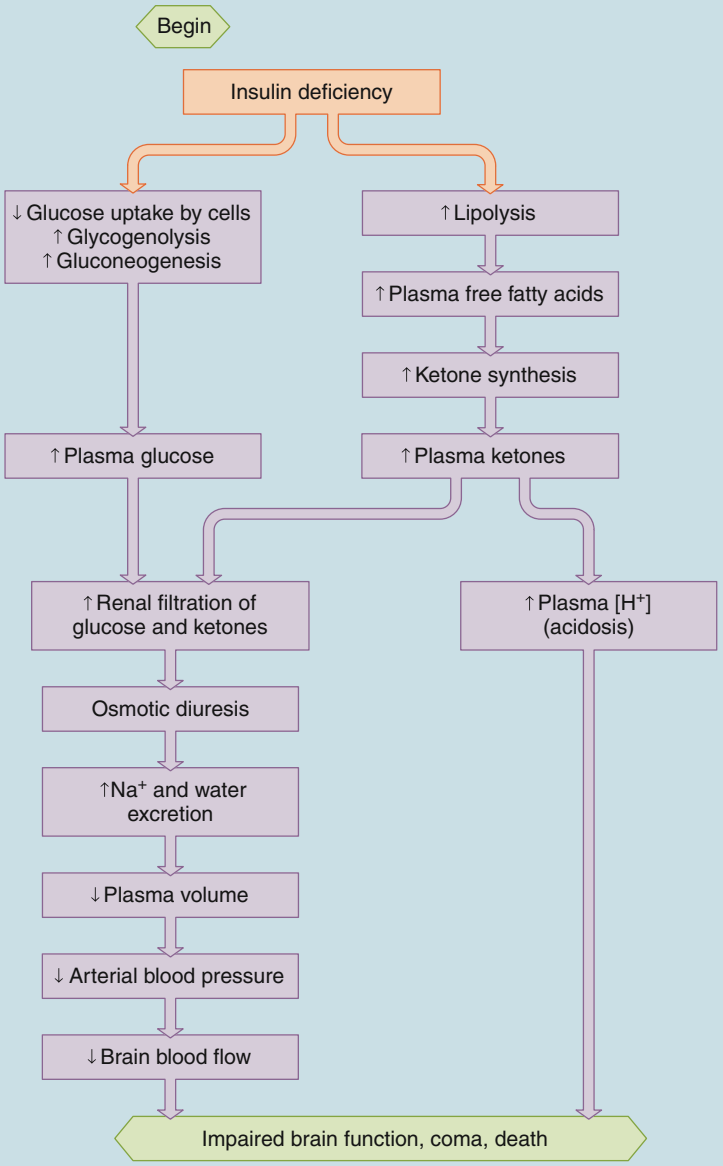


Figure 16.21 Diabetic ketoacidosis. Events caused by severe untreated insulin deficiency in type 1 diabetes mellitus.

the earlier mention of progressive weight loss in T1DM as a symptom of diabetes, why is it that most people with T2DM are overweight? One reason is that people with T2DM, in contrast to those with T1DM, do not excrete enough glucose in the urine to cause weight loss. Moreover, in T2DM, it is the excessive weight gain that contributes to the development of insulin resistance and impaired insulin secretion in diabetes.

Reflect and Review #2

- What is meant by target-cell hyporesponsiveness? Is it unique to insulin? (Refer back to the Clinical Case Study in Chapter 5 for details.)

Several factors combine to cause T2DM. One major problem is target-cell hyporesponsiveness to insulin, termed

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insulin resistance. Obesity accounts for much of the insulin resistance in T2DM, although a minority of people develop T2DM without obesity for reasons that are unknown. Obesity in any person—diabetic or not—usually induces some degree of insulin resistance, particularly in muscle and adipose-tissue cells. One hypothesis is that the excess adipose tissue overproduces messengers—perhaps inflammatory cytokines—that cause downregulation of insulin-responsive glucose transporters or in some other way blocks insulin's actions. Another hypothesis is that excess fat deposition in non-adipose tissue (for example, in muscle) causes a decrease in insulin sensitivity.

As stated earlier, many people with T2DM not only have insulin resistance but also have a defect in the ability of their beta cells to secrete insulin adequately in response to an increase in the concentration of plasma glucose. In other words, although insulin resistance is the primary factor inducing hyperglycemia in T2DM, an as-yet-unidentified defect in beta-cell function prevents these cells from responding maximally to the hyperglycemia. It is currently thought that the mediators of decreased insulin sensitivity described earlier may also interfere with a normal insulin secretory response to hyperglycemia.

The most effective therapy for obese persons with T2DM is weight reduction. An exercise program is also very important because insulin sensitivity is increased by frequent endurance-type exercise, independent of changes in body weight. This occurs, at least in part, because exercise causes a substantial increase in the total number of plasma membrane glucose transporters in skeletal muscle cells. Because a program of weight reduction, exercise, and dietary modification typically requires some time before it becomes effective, T2DM patients are usually also given orally active drugs that lower plasma glucose concentration by a variety of mechanisms. A recently approved synthetic incretin and another class of drugs called ***sulfonylureas*** lower plasma glucose concentration by acting on the beta cells to stimulate insulin secretion. Other drugs increase cellular sensitivity to insulin or decrease hepatic gluconeogenesis. Finally, in some cases, the use of high doses of insulin itself is warranted in T2DM.

Unfortunately, people with either form of diabetes mellitus tend to develop a variety of chronic abnormalities, including atherosclerosis, hypertension, kidney failure, blood vessel and nerve disease, susceptibility to infection, and blindness. Chronically increased plasma glucose concentration contributes to most of these abnormalities either by causing the intracellular accumulation of certain glucose metabolites that exert harmful effects on cells when present in high concentrations or by linking glucose to proteins, thereby altering their function. In our subject, the high glucose concentrations led to an accumulation of glucose metabolites in the lenses, causing them to swell due to osmosis; this, in turn, reduced the ability of his eyes to accurately focus light on the retina. He also had signs of nerve damage evidenced by the tingling sensations in his hands and feet. In many cases, symptoms such as his diminish or even disappear within days to months of receiving therapy. Nonetheless, over the long term, the aforementioned problems may still arise.

Our patient was counseled to begin a program of brisk walking for 30 minutes a day, at least five times a week, with the goal of increasing the duration and intensity of the exercise over the course of several months. He was also referred to a nutritionist, who advised him on a weight-loss program that involved a reduction in daily saturated fat, sugar, and total calories and increased consumption of fruits and vegetables. In addition, he was started immediately on two drugs, one that increases secretion of insulin from the pancreas and one that suppresses production of glucose from the liver. With time, the need for these drugs may be reduced and even eliminated if diet and exercise are successful in reducing weight and restoring insulin sensitivity.

Clinical terms: diabetes mellitus, diabetic ketoacidosis, insulin resistance, sulfonylureas, type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM)

See Chapter 19 for complete, integrative case studies.

CHAPTER 16 TEST QUESTIONS *Recall and Comprehend*

Answers appear in Appendix A.

These questions test your recall of important details covered in this chapter. They also help prepare you for the type of questions encountered in standardized exams. Many additional questions of this type are available on Connect and LearnSmart.

1. Which is *incorrect*?
   a. Fatty acids can be converted into glucose in the liver.
   b. Glucose can be converted into fatty acids in adipose cells.
   c. Certain amino acids can be converted into glucose by the liver.
   d. Triglycerides are absorbed from the GI tract in the form of chylomicrons.
   e. The absorptive state is characterized by ingested nutrients entering the blood from the GI tract.
2. During the postabsorptive state, epinephrine stimulates breakdown of adipose triglycerides by
   a. inhibiting lipoprotein lipase.
   b. stimulating hormone-sensitive lipase.
   c. increasing production of glycogen.
   d. inhibiting hormone-sensitive lipase.
   e. promoting increased adipose ketone production.
3. Which is true of strenuous, prolonged exercise?
   a. It results in an increase in plasma glucagon concentration.
   b. It results in an increase in plasma insulin concentration.
   c. Plasma glucose concentration does not change.
   d. Skeletal muscle uptake of glucose is inhibited.
   e. Plasma concentrations of cortisol and growth hormone both decrease.

4. Untreated type 1 diabetes mellitus is characterized by
   a. decreased sensitivity of adipose and skeletal muscle cells to insulin.
   b. higher-than-normal plasma insulin concentration.
   c. loss of body fluid due to increased urine production.
   d. age-dependent onset (only occurs in adults).
   e. obesity.
5. Which is *not* a function of insulin?
   a. to stimulate amino acid transport across cell membranes
   b. to inhibit hepatic glucose output
   c. to inhibit glucagon secretion
   d. to stimulate lipolysis in adipocytes
   e. to stimulate glycogen synthase in skeletal muscle
6. The calorigenic effect of thyroid hormones
   a. refers to the ability of thyroid hormones to increase the body's oxygen consumption.
   b. helps maintain body temperature.
   c. helps explain why hyperthyroidism is sometimes associated with symptoms of vitamin deficiencies.
   d. is the most important determinant of basal metabolic rate.
   e. All of the above are true.
7. Which of the following mechanisms of heat exchange results from local air currents?
   a. radiation
   b. convection
   c. conduction
   d. evaporation

True or False

8. Nonshivering thermogenesis occurs outside the thermoneutral zone.
9. Skin and core temperatures are both kept constant in homeotherms.
10. Leptin inhibits and ghrelin stimulates appetite.
11. Actively contracting skeletal muscles require more insulin than they do at rest.
12. Body mass index is calculated as height in meters divided by weight in kilograms.
13. In conduction, heat moves from a surface of higher temperature to one of lower temperature.
14. Skin blood vessels constrict in response to elevated core body temperature.
15. Evaporative cooling is most efficient in dry weather.

CHAPTER 16 TEST QUESTIONS *Apply, Analyze, and Evaluate*

Answers appear in Appendix A.

These questions, which are designed to be challenging, require you to integrate concepts covered in the chapter to draw your own conclusions. See if you can first answer the questions without using the hints that are provided; then, if you are having difficulty, refer back to the figures or sections indicated in the hints.

1. What happens to the triglyceride concentrations in the plasma and in adipose tissue after administration of a drug that blocks the action of lipoprotein lipase? *Hint:* Look at Figure 16.1 and imagine where lipoprotein lipase acts in that figure.
2. A person has a defect in the ability of her small intestine to reabsorb bile salts. What effect will this have on her plasma cholesterol concentration? *Hint:* Refer back to Figure 15.32 and associated text, and to Figure 16.2.
3. A well-trained athlete is found to have a moderately increased plasma total cholesterol concentration. What additional measurements would you advise this person to take in order to gain a better understanding of the importance of the increased cholesterol? *Hint:* Think about the forms in which cholesterol exists in blood.
4. A resting, unstressed person has increased plasma concentrations of free fatty acids, glycerol, amino acids, and ketones. What situations might be responsible and what additional plasma measurement would distinguish among them? *Hint:* See Section 16.2 and the Clinical Case Study.
5. A healthy volunteer is given an injection of insulin after an overnight fast. Soon after, the plasma concentrations of which hormones increase as a result? *Hint:* See Figures 16.10 and 16.11 and Tables 16.3 and 16.4.
6. If the sympathetic preganglionic fibers to the adrenal medulla were cut in an animal, would this eliminate the sympathetically mediated component of increased gluconeogenesis and lipolysis during exercise? Explain. *Hint:* See Figure 16.11.
7. What are the sources of heat loss for a person immersed up to the neck in a 40°C bath? *Hint:* See Figure 16.17, and recall that body temperature is about 37°C.

CHAPTER 16 TEST QUESTIONS *General Principles Assessment*

Answers appear in Appendix A.

These questions reinforce the key theme first introduced in Chapter 1, that general principles of physiology can be applied across all levels of organization and across all organ systems.

1. A general principle of physiology is that *most physiological functions are controlled by multiple regulatory systems, often working in opposition.* How is this principle illustrated by the pancreatic control of glucose homeostasis? (*Note:* Compare Figures 16.5, 16.8, and 16.10 for help.)
2. This same principle also applies to the control of appetite. Give at least five examples of factors that regulate appetite in humans, including some that stimulate and some that inhibit appetite.
3. Body temperature homeostasis is critical for maintenance of healthy cells, tissues, and organs. Using Figure 16.17 as your guide, explain how the control of body temperature reflects the general principle of physiology that *physiological processes are dictated by the laws of chemistry and physics.*

CHAPTER 16 ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS

Figure 16.1 Eating a diet that is low in fat content does not mean that a person cannot gain additional adipose mass, because as shown in this figure, glucose and amino acids can be converted into fat in the liver. From there, the fat is transported and deposited in adipose tissue. A diet that is low in fat but rich in sugar, for example, could still result in an increase in fat mass in the body.

Figure 16.3 During the postabsorptive state, energy-yielding molecules are moved between all the organs of the body such that energy is supplied during periods when food is not available. For example, note in Figure 16.3 how glucose is moved from the liver to the blood and from there to all cells, where it is metabolized to yield energy. Similarly, fatty acids circulate from adipose tissue to other cells and serve as another source of energy. The shuttling of matter (organic molecules) between organs, including its utilization for energy, is a fundamental feature of homeostasis in humans. See Figure 16.1, however, for the reverse process— namely, the *storage* of energy in different organs.

Figure 16.6 Having the transporters already synthesized and packaged into intracellular vesicle membranes means that glucose transport can be tightly and quickly coupled with changes in glucose concentrations in the blood. This protects the body against the harmful effects of excess blood glucose concentrations and also prevents urinary loss of glucose by keeping the rate of glucose filtration below the maximum rate at which the kidney can reabsorb it. This tight coupling could not occur if the transporters were required to be synthesized each time a cell was stimulated by insulin.

Figure 16.8 The brain is absolutely necessary for immediate survival and can maintain glucose uptake from the plasma in the fasted state when insulin concentrations are very low.

Figure 16.10 Fight-or-flight reactions result in an increase in sympathetic nerve activity. These neurons release norepinephrine from their axon terminals (see Chapter 6), which stimulates glucagon release from the pancreas. Glucagon then contributes to the increase in energy sources such as glucose in the blood, which facilitates fight-or-flight reactions.

Figure 16.14 The body's normal response to leptin is to decrease appetite and increase metabolic rate. This would not be adaptive during times when it is important to increase body energy (fat) stores. An example of such a situation is pregnancy, when gaining weight in the form of increased fat mass is important for providing energy to the growing fetus. In nature, another example is the requirement of hibernating animals to store large amounts of fat prior to hibernation. In these cases, the effects of leptin are decreased or ignored by the brain.

Figure 16.15 In the short term, drinking water before a meal may decrease appetite by stretching the stomach, and this may contribute to eating a smaller meal. However, as described in Chapter 15, water is quickly absorbed by the GI tract and provides no calories; thus, hunger will soon return once the meal is over.

Figure 16.17 The amount of fluid in the body decreases as water evaporates from the surface of the skin. This fluid must be replaced by drinking or the body will become dehydrated. In addition, sweat is salty (as you may have noticed by the salt residue remaining on hats or clothing once the sweat has dried). This means that the body's salt content also needs to be restored. This is a good example of how maintaining homeostasis for one variable (body temperature) may result in disruption of homeostasis for other variables (water and salt).

Figure 16.19 At least four organ systems contribute in a coordinated way to the production of fever during infection: the immune system (secretion of pyrogens); the nervous system (temperature set point and signals to muscles and blood vessels); the musculoskeletal system (shivering); and the circulatory system (vasoconstriction).

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