The Endocrine System: Regulation of Energy Metabolism and Growth

Have you ever been stuck in classes from 10:00 until 1:00? If so, you probably had difficulty concentrating part of the time because you started feeling hungry before that last class let out. At 1:30, however, you replenished your energy reserves by eating a late lunch. That allowed you to study until 6:00 before the next wave of hunger set in.

Energy balance differs from other body balances because energy input from meals is intermittent. This uneven input creates a challenge for our organ systems, but the challenge is met through the actions of primarily two hormones, insulin and glucagon. You will learn in this chapter how insulin and glucagon regulate energy metabolism to maintain adequate glucose for our neurons to function. You will also learn how other hormones affect energy metabolism as the body grows or copes with stress.

COLORIZED LIGHT MICROGRAPH OF A FOLLICLE IN THE THYROID GLAND.

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CHAPTER 21 The Endocrine System: Regulation of Energy Metabolism and Growth

Before You Begin
Make sure you have mastered the following topics:

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- Metabolic pathways, p. 57
- Glycolysis, p. 74
- Krebs cycle, p. 75
- Electron transport chain, p. 78
- Pancreas, p. 155
- Thyroid gland, p. 154
- Hypothalamus-anterior pituitary tropic hormones, p. 152
- Adrenal glands, p. 154
- Muscle metabolism, p. 340

Early in this text (in Chapter 3), we explored cellular metabolism, including mechanisms for generating the adenosine triphosphate (ATP) that our cells need to perform work. In subsequent chapters, we learned how cells work together as tissues and organs to perform particular tasks, the coordinated activity of which maintains homeostasis. Whole-body metabolism is regulated primarily by hormones (whose basic properties were discussed in Chapter 6). In this chapter, we examine the coordinated regulation of metabolic pathways in different organs to maintain adequate energy supplies for all the body’s cells, focusing on hormonal control of energy balance.

As we study these hormones and their actions, we will find that their effects are varied and often overlap. To help you understand these hormones, the first section of this chapter presents general principles relating to energy metabolism and energy balance. A comparison of energy metabolism during and between meals follows. The chapter then describes the hormones that regulate blood glucose level, especially insulin and glucagon. The next section covers thermoregulation, a process closely linked to energy metabolism. The hormones that regulate growth and the primary hormones that regulate whole-body metabolism—thyroid hormones—are then discussed. The final section of the chapter describes the glucocorticoids and their role in adapting to stress.

21.1 An Overview of Whole-Body Metabolism

The next time you find yourself sitting down to eat a meal, ask yourself this question: Why am I eating? If you do this on several occasions, you will find that many possible reasons for eating exist.

Perhaps you smelled something cooking that stimulated your appetite, or you saw an advertisement for a food you like. Perhaps you decided to join some friends who were on their way to dinner, or maybe you just looked at your watch and decided it was mealtime. The number of possibilities is large. In fact, we have so many different motivations for eating that it is easy to forget that the ultimate reason—obtaining nutrition—is a biological necessity, because food is our sole source of energy and the raw materials from which our bodies are made.

Although biological necessity drives our need for food, our eating patterns vary and are influenced by other factors. (You have probably skipped meals to study for exams or have overeaten during the holidays.) In most cases, this inconsistency is no cause for concern because the body has ways of maintaining the steady supply of energy that cells need despite changes in the pattern of food intake. Between meals the body converts energy stores (including large carbohydrates, proteins, and lipids) into smaller molecules that cells can use for energy. When you eat, the body replenishes these stores by converting nutrients into energy storage molecules.

The way the body stores and utilizes energy—energy metabolism—is influenced not only by eating patterns but also by such factors as growth, stress, and metabolic rate. In all cases, whether the body stores or utilizes energy is controlled primarily by endocrine signals. Two critical concepts drive the control of energy metabolism:

1. Because food intake is intermittent, the body must store nutrients during periods of intake and then break down these stores during periods between meals.
2. Because the brain depends on glucose as its primary energy source, blood glucose levels must be maintained at all times, even between meals.

To fully appreciate the control of metabolism, we need to review some key concepts of cellular metabolism (first described in Chapter 3) and relate them to the whole body.

Anabolism

An interesting aspect of metabolism is that the same small biomolecules that provide energy are also used to synthesize larger biomolecules. A good example is acetyl CoA (described in Chapter 3), which can be catabolized in the Krebs cycle for energy and also serves as a substrate for triglyceride and cholesterol synthesis. Thus, because carbohydrates, lipids, and proteins can all be catabolized to
acetyl CoA, they can all eventually be converted to lipids. Many other metabolic intermediates of glycolysis and the Krebs cycle can be used to synthesize larger biomolecules. For example, some metabolic intermediates can be converted to amino acids and used for protein synthesis, whereas other intermediates can be used in the synthesis of phospholipids.

**Regulation of Metabolic Pathways**

If anabolic and catabolic pathways have several of the same intermediates, what governs the direction of metabolism? The most important factors in determining which metabolic pathways are in operation are the number and activity of the enzymes involved in the pathways. The activity of enzymes can be regulated by changing their concentration through synthesis or degradation, or by changing the activity of individual enzyme molecules through allosteric or covalent regulation. Hormones that regulate metabolic pathways do so by regulating the activity of enzymes in one or more of these ways.

Metabolic pathways are also controlled by compartmentation. Cellular compartmentation was described earlier in this text (in Chapter 3): Whereas glycolysis occurs in the cytosol, the Krebs cycle occurs in the mitochondrial matrix. Compartmentation also occurs on the tissue level, because some enzymes are found in the cells of only certain tissues. In addition, hormones differentially affect tissues based on the types of receptors on the cells in that tissue. Tissues or organs that have special metabolic activities include the brain, skeletal muscle, the liver, and adipose tissue. We will explore how these tissues and organs affect whole-body metabolism shortly; first we consider how the body handles different classes of biomolecules, from absorption, to cellular uptake, to utilization by the cell.

**21.2 Energy Intake, Utilization, and Storage**

When we eat, digestion in the gastrointestinal (gi) tract breaks down the large molecules in food into smaller molecules, which are then absorbed into the bloodstream. Of our three main nutrient classes, carbohydrates are transported in the blood as glucose, proteins are transported as amino acids, and lipids are transported in lipoproteins. The blood flow distributes these nutrients to tissues throughout the body, where they are eventually taken up by cells. Inside cells, these molecules undergo one of three possible fates:

1. Biomolecules can be broken down into smaller molecules, in the process releasing energy that can be used for driving various cellular processes such as muscular contraction, transport, secretion, or anabolism.
2. Biomolecules can be used as substrates to synthesize other molecules needed by cells and tissues for normal function, growth, and repair.
3. Biomolecules in excess of those required for energy and synthesis of essential molecules are converted to energy storage molecules that provide energy during periods between meals. The two primary energy storage molecules are glycogen and triglyceride (fat).

The ultimate fate of consumed molecules depends on their chemical nature and the body’s needs at the time of consumption, as described next.

**Uptake, Utilization, and Storage of Energy in Carbohydrates**

Although carbohydrates are consumed in a variety of forms, mono- saccharides—especially glucose—are the forms found in the bloodstream. Figure 21.1a illustrates the fate of glucose in the blood. Molecules of glucose are transported into cells throughout the body by glucose transporters. Inside cells, glucose can be oxidized for energy, which generates carbon dioxide as a waste product; can provide substrates for other metabolic reactions; or can be converted to glycogen for storage. If glucose levels in the cell decrease, glycogen can be broken down to glucose by glycogenolysis.

Although this series of steps accurately describes what happens to glucose in the body as a whole, it may or may not describe what happens in individual cells. Most cells, for example, can oxidize glucose but have a limited ability to synthesize and store glycogen.

**Uptake, Utilization, and Storage of Energy in Proteins**

As depicted in Figure 21.1b, amino acids rather than whole proteins are transported in the bloodstream. Following uptake into cells, amino acids are used for the synthesis of proteins, or catabolized for energy by proteolysis. Because proteins consist of amino acids, protein catabolism produces amino acids, which can then be catabolized for energy or released into the bloodstream for use by other cells. Cells utilize protein catabolism for energy less so than carbohydrates and lipids, but when proteins are used, ammonia and carbon dioxide are produced. The highly toxic ammonia is converted by the liver to urea, which is eventually eliminated in the urine.

**Uptake, Utilization, and Storage of Energy in Fats**

When the body uses dietary carbohydrates and proteins, they are taken into cells in the form of smaller components (glucose or amino acids), which can either be catabolized for energy or assembled into larger molecules. The same process occurs for fats, although the process is a little more complicated.

Figure 21.1c illustrates the body’s handling of triglycerides, the predominant form in which fats are present in the diet. Triglycerides are transported in the bloodstream in lipoproteins, small protein- and lipid-containing particles. An assortment of lipoproteins of varying densities transports lipids to various target cells throughout the body (see Chapter 20, Discovery: Lipoproteins and Plasma Cholesterol, p. 586). Once they reach their target cells, lipids must leave the lipoprotein before they can enter the cells.

To facilitate entry into cells, triglycerides at the outer surface of lipoproteins are broken down by the enzyme lipoprotein lipase.
which is located on the inside surface of capillaries throughout the body and is particularly dense in capillaries running through adipose tissue (body fat). This enzyme breaks down triglycerides into fatty acids and monoglycerides; the fatty acids are then taken up by nearby cells (b), while the monoglycerides remain in the bloodstream and are eventually metabolized in the liver.

After entering cells, fatty acids may be oxidized for energy (c) or combined with glycerol to form new triglycerides (d), which are stored in fat droplets in the cytosol. This storage occurs mainly in adipocytes, adipose tissue cells that are specialized for fat storage. (The glycerol used in triglyceride synthesis is not derived from adipocytes, stored in fat droplets in the cytosol. This storage occurs mainly in adipose tissue cells that are specialized for fat storage.) Stored triglycerides can subsequently be broken down into absorbed triglycerides, but instead is synthesized within adipocytes. (The glycerol used in triglyceride synthesis is not derived from adipocytes, stored in fat droplets in the cytosol. This storage occurs mainly in adipose tissue cells that are specialized for fat storage.)

Table 21.1 summarizes the body’s processing of carbohydrates, proteins, and lipids. Fatty acids are included among the smaller nutrient molecules (even though they are not absorbed in this form) because they are the form in which fats are made available to most cells. Some small nutrients can be interconverted; for example, glucose can be synthesized from amino acids, and fatty acids can be synthesized from glucose or amino acids. These interconversions have a significant role in whole-body metabolism, as we will see shortly.

21.3 Energy Balance

To maintain homeostasis, the human body must be kept in balance. To be “in balance” in this context means that what comes into the body and what is produced by the body equal the sum of what is used by the body and what is eliminated by the body. This relationship is summarized in the following equation:

\[ \text{Input} + \text{production} = \text{utilization} + \text{output} \]

In terms of energy balance, the body does not produce energy (an impossibility according to the laws of thermodynamics) and so this equation becomes

\[ \text{Energy input} = \text{energy utilization} + \text{energy output} \]

Energy is used by the body to perform work, and energy output exists as heat released. Therefore, the balance equation becomes

\[ \text{Energy input} = \text{work performed} + \text{heat released} \]

The endocrine system regulates the body’s energy balance to ensure that a steady supply of small nutrients is always available to all cells to meet their energy demands. As cells expend energy, they draw on stores of nutrients both within cells and in the bloodstream to obtain more energy. This pool of nutrients must be continually replenished if uninterrupted energy expenditure is to occur. This replenishment can be accomplished in two ways: by absorption of
more nutrients into the bloodstream or by mobilization of energy stores—that is, the catabolism of stored macromolecules into small nutrient molecules that are released into the bloodstream. The body mobilizes its energy stores when the rate of energy intake is insufficient to meet its energy needs.

### Energy Input

Energy input into the body arrives in the form of absorbed nutrients. When a particular nutrient molecule (such as glucose) is oxidized in the body, a certain quantity of energy is liberated; this quantity represents the energy content of the molecule. A person’s energy intake is the total energy content of all nutrients absorbed.

The energy content of a nutrient is generally determined by burning a known quantity of the substance in an instrument called a calorimeter, which measures the total amount of energy released in the form of heat as the substance burns. This amount is usually expressed in kilocalories per gram of the substance burned. Kilocalories can also be written as Calories, with a capital C (1 kilocalorie = 1 Calorie = 1000 calories). The energy content of nutrient molecules varies for the three nutrient classes, averaging 4 Calories per gram of carbohydrates, 4 Calories per gram of protein, and 9 Calories per gram of fat. Thus fat, which has a higher energy content than carbohydrates and proteins, is the most efficient form in which to store energy.

### Energy Output

In a calorimeter, all the energy contained in a molecule is converted to heat during oxidation, so that the energy content of the molecule (input) is equal to the quantity of energy in the heat (output). Although the body also relies on the oxidation of molecules to liberate energy, the energy released during oxidation or other catabolic reactions always takes two forms: heat and work (Figure 21.2). Approximately 60% of the energy in consumed nutrients goes to heat production, which is necessary to maintain body temperature. Most of the remaining 40% of energy is used to synthesize ATP, which is used to perform cellular work (a process that releases still more heat).

The energy-requiring processes of cells are classified into three main categories: mechanical, chemical, and transport. Mechanical work uses intracellular protein filaments to generate movement, such as occurs in muscle contraction or the beating of cilia lining the respiratory tract. Chemical work is used to form bonds during chemical reactions, such as the bond formation that occurs when small molecules are used to synthesize large molecules. Transport work utilizes energy to move a molecule from one side of a cell membrane to another, such as occurs in active transport (the Na⁺/K⁺ pump, for example) or in vesicular transport (exocytosis and endocytosis).

### Metabolic Rate

When the body breaks down nutrients, it either releases energy as heat or uses that energy to perform work. The amount of energy so expended per unit time is the body’s metabolic rate. A person’s metabolic rate is influenced by a number of factors, including muscular activity, age, gender, body surface area, and environmental temperature. When sitting still, for example, the rate of energy expenditure is approximately 100 kilocalories per hour; when riding a bicycle at a moderate rate, it tops 300 kilocalories per hour.

The basal metabolic rate (BMR) is the rate of energy expenditure of a person who has fasted for at least 12 hours and is awake, lying down, and physically and mentally relaxed; under these conditions, both metabolic rate and work performed are minimal. The BMR is usually estimated by measuring a person’s rate of oxygen consumption, which correlates with the rate at which nutrients are oxidized in the body.

The BMR represents the energy requirement of performing such necessary tasks as pumping blood and transporting ions. This rate generally increases as body weight increases, because a larger mass of tissue requires greater energy expenditure for its upkeep; therefore, the BMR is usually expressed as the rate of energy expenditure per unit body weight. For adults, it averages 20–25 kilocalories per kilogram of body weight per day. Most of this expenditure is due to activity in the nervous system and skeletal muscles, which account for 40% and 20–30% of the BMR, respectively. The BMR

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**TABLE 21.1** Summary of Carbohydrates, Protein, and Lipid Processing

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Form absorbed across GI tract</th>
<th>Form circulating in blood</th>
<th>Form stored</th>
<th>Storage site</th>
<th>Percentage of total energy stored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrates</td>
<td>Glucose</td>
<td>Glucose</td>
<td>Glycogen</td>
<td>Liver, skeletal muscle</td>
<td>1%</td>
</tr>
<tr>
<td>Proteins</td>
<td>Amino acids, some small peptides</td>
<td>Amino acids</td>
<td>Proteins</td>
<td>Skeletal muscle*</td>
<td>22%</td>
</tr>
<tr>
<td>Lipids</td>
<td>Monoglycerides and fatty acids (in chylomicrons)</td>
<td>Free fatty acids, lipoproteins</td>
<td>Triglycerides</td>
<td>Adipose tissue</td>
<td>77%</td>
</tr>
</tbody>
</table>

*Even though proteins are found in all cells of the body, most of the proteins that are mobilized for energy come from skeletal muscle cells.

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**Figure 21.2** The forms of energy produced by the oxidation of nutrient molecules. Some of the energy liberated during oxidation is used to generate ATP, which can perform various types of work within cells; the rest of the energy takes the form of heat.
varies from tissue to tissue; muscle tissue, for example, has a higher resting metabolic rate than adipose tissue. The BMR (per unit body weight) also varies with age: It is greater in growing children because of the energy expended in the synthesis of new tissue, and it is usually lower in the elderly than in young adults.

**Apply Your Knowledge**

Notice that the BMR is lowest when a person is awake, not asleep. Explain this phenomenon based on what you previously learned about sleep (in Chapter 9).

**Negative and Positive Energy Balance**

In today’s society, virtually everyone is aware that body weight, diet, and exercise are interrelated. When people eat a lot of food but do not get much exercise, their body weight tends to increase; when they eat less and exercise more, their body weight decreases. These changes in body weight occur when energy input and output are not balanced.

If the body is not in energy balance—that is, if energy input and energy output are not equal—then the difference between energy input and output determines whether the amount of stored energy increases or decreases. From our balance equation, we can determine the amount of energy that is stored:

\[
\text{Energy stored} = \text{energy input} - \text{energy output} \\
= \text{energy input} - (\text{work performed} + \text{heat released})
\]

When a person takes in energy at a rate greater than he or she expends energy as heat and work, the quantity of stored energy increases. This condition, called **positive energy balance**, tends to be associated with increases in body weight; a net synthesis of macromolecules from absorbed nutrients occurs. (Later in this chapter we see that most excess nutrients are converted to lipids for storage.) When the rate of energy intake is less than the rate at which energy is expended as heat or work, the quantity of stored energy decreases. This condition, known as **negative energy balance**, tends to be associated with decreases in body weight. Under these conditions, a net breakdown of macromolecules (including lipid stores) provides energy for body functions.

When someone goes on a diet to lose weight, the idea is to decrease food intake and achieve negative energy balance. The same result can be attained through exercise, which increases work and heat production (energy output). To learn more about how energy is metabolized during exercise, see **Understanding Exercise: Energy Metabolism**.

Although the concept of energy balance is useful for explaining why diet and exercise affect body weight, note that a change in the body’s energy content is not necessarily equivalent to a change in mass. If during a given time span 100 grams of glucose is absorbed and 100 grams of triglycerides is oxidized, then body weight does not change; however, the body’s energy content decreases because 1 gram of glucose contains less energy than 1 gram of triglycerides.

**Quick Check 21.1**

1. What are the storage forms of carbohydrates and lipids?
2. Once energy is taken into the body, either it is stored or else it appears in which two other forms?

**21.4 Energy Metabolism During the Absorptive and Postabsorptive States**

We have seen that maintaining energy balance requires that energy input equal energy output. However, the body is generally not in energy balance at any given time, because the rate of energy input is determined by feeding, which is intermittent. For approximately 3–4 hours after a typical meal, nutrients are absorbed during the **absorptive state**, after which time absorption stops until the next meal. During this time, the rate of energy input generally exceeds energy output, putting the body in positive energy balance. Nutrients in the blood are plentiful. Glucose serves as the primary energy source for cells, while fats, amino acids, and excess glucose are taken up by liver, muscle, and fat cells and converted to energy storage molecules. The **postabsorptive state** corresponds to the time between meals, when nutrients are not being absorbed; during this time, the rate of energy expenditure is greater than the rate of energy intake. Energy stores are mobilized to provide the energy needs. Whereas glucose serves as the energy source for cells in the central nervous system, other cells in the body utilize other energy sources (such as fatty acids), thereby sparing glucose for the central nervous system.

Energy metabolism during the absorptive and postabsorptive states can be summarized by the following rule: **During the absorptive state, energy is stored in macromolecules; during the postabsorptive state, these energy stores are mobilized**. This rule is important because it means that although we might eat different amounts of nutrients at different times, the body provides a constant supply of nutrients to cells—a supply that cannot be interrupted for even a minute because the body must expend energy continuously just to stay alive. In the following sections we see how the body performs this necessary function.

**Metabolism During the Absorptive State**

The absorptive state is primarily an anabolic state—that is, the majority of reactions involve synthesis of macromolecules. However, cellular metabolism differs among cell types. In this subsection we explore the typical absorptive state metabolic responses in body cells in general, in skeletal muscle cells, in liver cells, and in adipocytes (Figure 21.3).

**Body Cells in General**

The body’s energy needs are supplied primarily by absorbed glucose, which is plentiful after a typical meal. Glucose is taken into the cells and catabolized as the body’s primary fuel. Absorbed fatty acids and amino acids can also be catabolized for energy, particularly if the diet is rich in these nutrients but poor in carbohydrates. Fatty
acids undergo oxidation to provide acetyl CoA subunits for the Krebs cycle, and amino acids are converted to keto acids (organic acids with a carbonyl group, C=O), many of which serve as intermediates for the Krebs cycle. Amino acids can also be used to synthesize proteins.

Note, however, that proteins are not synthesized as “storage molecules.” Instead, most body proteins have important structural and functional roles in cells and are continuously turned over; that is, old proteins are degraded and replaced with new ones. For this reason, the body’s protein mass remains relatively stable and does not increase simply in response to the absorption of an excess of amino acids. Body cells catabolize proteins for energy only under extreme conditions, because doing so comes at the expense of losing functioning molecules.

Skeletal Muscle Cells
Like body cells in general, skeletal muscle cells take up glucose and amino acids from the blood for their own needs. However, unlike most body cells, skeletal muscle cells can convert glucose to...
glycogen for storage. Within individual muscle cells, these glycogen stores are limited, but taken together they constitute the majority (approximately 70%) of the body’s total stored glycogen.

**Liver Cells**

The liver converts nutrient molecules to energy stores that can subsequently be mobilized to supply energy to most cells in the body. The liver converts glucose to glycogen or fatty acids, and fatty acids to triglycerides. The glycogen is stored in the liver (which contains approximately 24% of the body’s glycogen stores), whereas the triglycerides are transported to adipose tissue for storage. Between liver and skeletal muscle, the body can store a maximum of approximately 500 grams of glycogen, an amount that is sufficient to meet the body’s energy demands for only a few hours. Any absorbed glucose that exceeds the quantity that is needed for energy or that can be stored as glycogen is converted first to fatty acids and then to triglycerides.

The liver also takes up amino acids. Although the liver uses some amino acids to synthesize proteins (including plasma proteins), most amino acids are converted to keto acids, many of which act as intermediates in glycolysis or the Krebs cycle and can be used for energy. Most of the keto acids, however, are used to synthesize fatty acids; thus they ultimately end up as triglycerides.

The triglycerides synthesized in the liver must be transported to adipose tissue, which is achieved by packaging the triglycerides into particles called **very low density lipoproteins (VLDLs)**. (See Chapter 20, Discovery: Lipoproteins and Plasma Cholesterol, p. 586.) Briefly, VLDLs transport triglycerides to the cells of the body. The plasma membranes of most cells contain the enzyme lipoprotein lipase, which catalyzes triglycerides at the outer surface of the VLDLs to fatty acids and monoglycerides. The fatty acids then diffuse into cells, where they can be used for energy (by most body cells) or converted back into triglycerides for storage (in adipocytes). Adipocytes have a high concentration of lipoprotein lipase on their plasma membranes and, therefore, take up most of the fatty acids transported in VLDLs.

**Adipocytes**

Adipocytes store energy in the form of triglycerides, or fat. Absorbed triglycerides are transported to adipocytes by chylomicrons, the smallest of the lipoproteins. Lipoprotein lipase catalyzes the triglycerides in chylomicrons in the same manner as just described for VLDLs. Excess absorbed glucose enters the adipocytes and is converted to triglycerides. In addition, triglycerides synthesized in the liver are transported to adipocytes by VLDLs for storage.

**Energy Reserves**

Whereas the body is limited in its ability to store energy in the form of glycogen or protein, it is practically unlimited in its ability to store energy as fats. As a consequence, triglyceride synthesis represents the final common pathway for all nutrients that are absorbed in excess of the body’s needs. In most people, fat accounts for 20–30% of total body weight, but in very overweight individuals it can account for as much as 80%. To people who are weight conscious, the body’s propensity for storing nutrients as fats is at best an annoyance. However, given that triglycerides contain more energy than carbohydrates or proteins, triglyceride synthesis is clearly the best way to store the most energy in the least weight.

Under normal circumstances, glycogen stores account for 1% or less of the body’s total energy reserves and can supply a person’s energy needs for only a few hours of quiet activity. Proteins account for 20–25% of the total energy reserves. Although large amounts of protein can be mobilized for energy without serious consequences, particularly from skeletal muscle, continual use of protein for energy is harmful and potentially fatal because it eventually compromises cellular function. Thus a significant portion of the energy contained in protein stores is, in reality, unavailable for use.

Fat stores represent 75–80% of the total energy reserves and contain enough energy to sustain human life for approximately two months. For this reason, fats are absolutely essential to the body’s ability to withstand prolonged periods of fasting. Table 21.2 tabulates the average energy stores of a healthy man weighing about 154 lbs.

### Metabolism During the Postabsorptive State

Within a few hours after a typical meal, absorption of nutrients ceases. Without absorbed nutrients for energy, the body catabolizes glycogen, proteins, and fats to meet its energy needs (Figure 21.4). Thus the postabsorptive state is primarily a catabolic state. In addition, unlike most body cells, central nervous system cells rely on glucose as their sole energy source (cells of the central nervous system can also obtain energy from ketone bodies during extreme conditions). Therefore, a primary function of the postabsorptive state is to maintain plasma glucose levels. Too large a reduction in plasma glucose can result in serious impairment of brain function, loss of consciousness, and even death.

Given the importance of maintaining a steady supply of glucose during the postabsorptive state, a question naturally arises: Because glucose is derived from the breakdown of glycogen, which is in relatively short supply (enough to last only a few hours), how is glucose made available for longer periods? The body synthesizes new glucose from amino acids, glycerol, and other breakdown products of catabolism, a process known as **gluconeogenesis**. In addition, most tissues turn almost exclusively to other energy sources, primarily fatty acids, thereby conserving glucose for use by the central nervous system; this process is called **glucose sparing**.

As in the absorptive state, cellular metabolism during the postabsorptive state differs among the types of cells.

### TABLE 21.2 Energy Stores (as a Percentage of Total Energy Reserves) in a Healthy, Approximately 154-lb. Man

<table>
<thead>
<tr>
<th></th>
<th>Glycogen</th>
<th>Triglycerides</th>
<th>Proteins (mobilizable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle</td>
<td>71</td>
<td>&lt;1</td>
<td>98</td>
</tr>
<tr>
<td>Liver</td>
<td>24</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>5</td>
<td>99</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Brain</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Liver Cells

The liver is the primary source of plasma glucose during the postabsorptive state. Its glycogen stores can be broken down by glycogenolysis to glucose-6-P, and its supply of glucose-6-phosphatase then catalyzes the conversion of glucose-6-P to glucose. This glucose can, in turn, be transported out of the liver cells and into the bloodstream. Therefore, liver glycogen stores, unlike skeletal muscle glycogen stores, can be mobilized to provide glucose to the blood.

The liver is also the primary site of gluconeogenesis. (Some gluconeogenesis does occur in the kidneys, which also produce the enzyme glucose-6-phosphatase.) Like the glucose produced by glycogenolysis, the newly synthesized glucose is transported from the liver into the bloodstream for use by other cells in the body.

During the postabsorptive state, **ketogenesis** occurs in the liver; during this process, some of the fatty acids are converted to ketone bodies, which are then released into the bloodstream and eventually catabolized by most tissues. The production of ketones is important because during prolonged fasting, the central nervous system acquires the ability to use ketones for energy, thereby freeing it from some of its dependence on glucose.
The Role of Insulin

The metabolic adjustments that occur as the body switches between the postabsorptive and absorptive states are largely triggered by changes in the plasma concentration of insulin, a peptide hormone secreted by beta cells located in the pancreatic islets of Langerhans (see Chapter 6). Even though insulin and the factors that influence its secretion exert numerous effects, they all share a common thread: **Insulin promotes the synthesis of energy storage molecules and other processes characteristic of the absorptive state** (Figure 21.5). In other words, insulin is an anabolic hormone. Accordingly, its secretion is stimulated by signals associated with feeding and the absorption of nutrients into the bloodstream.

Factors Affecting Insulin Secretion

During the absorptive period, insulin secretion by beta cells increases, causing plasma insulin levels to increase, and promoting many of the metabolic processes characteristic of the absorptive state. During the postabsorptive state, insulin secretion decreases, causing a decrease in the plasma concentration of insulin, which helps turn off the absorptive processes. This raises a key question: How do beta cells know when to increase or decrease insulin secretion?

Table 21.3 shows that several factors influence insulin secretion. Particularly important among these is plasma glucose concentration. During the absorptive period, plasma glucose levels increase as glucose is transported into the bloodstream from the GI tract. This increase stimulates insulin secretion through a direct effect of glucose on beta cells, which are sensitive to the concentration of glucose in the fluid surrounding them (Figure 21.6). Glucose enters beta cells by facilitated diffusion utilizing GLUT2 transporters. Glucose is catabolized in a process that generates ATP, which then closes potassium channels in the beta cell membrane. With less potassium moving out, the beta cell becomes depolarized,
response to the presence of food in the GI tract. Given that feeding occurs prior to the absorption of nutrients, these feedforward signals prepare the body for transitioning to the absorptive state by triggering insulin secretion in advance of rising plasma glucose levels. Insulin secretion is inhibited by sympathetic nervous activity and circulating epinephrine.

**Actions of Insulin**

Through its actions on a variety of target tissues, insulin influences almost every major aspect of energy metabolism (see Figure 21.5). It promotes energy storage by stimulating the synthesis of fatty acids and triglycerides in the liver and adipose tissue, glycogen in liver and skeletal muscle, and proteins in most tissues. At the same time, it opposes the catabolism of energy stores by inhibiting the breakdown of proteins, triglycerides, and glycogen, and by suppressing gluconeogenesis by the liver. In short, insulin promotes reactions associated with the absorptive state and suppresses reactions linked to the postabsorptive state.

Along with its metabolic actions, insulin affects the transport of nutrients across the membranes of all body cells except those in the liver and central nervous system. In most tissues, insulin stimulates the uptake of amino acids by cells, which facilitates the hormone's stimulatory effect on protein synthesis. There are at least four insulin-sensitive active transporters that move at least eight of the nonessential amino acids from plasma into cells, thereby decreasing amino acid levels in the plasma. Uptake of amino acids into cells varies based on cell type, with uptake into skeletal muscle cells occurring to the greatest extent.

**Figure 21.6** Actions of glucose on insulin secretion.

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**TABLE 21.3 Factors Affecting Insulin and Glucagon Release**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on insulin secretion</th>
<th>Effect on glucagon secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Plasma [glucose]</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>↑ Plasma [amino acids]</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>↑ Plasma [GIP]</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>↑ Parasympathetic activity</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>↑ Sympathetic activity</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>↑ Plasma [epinephrine]</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
</tbody>
</table>
Insulin also stimulates the uptake of glucose in some tissues by increasing the number of glucose transport proteins in cell plasma membranes. Thirteen different glucose transporters are coded in the human genome, called GLUT1 through GLUT13. (We saw earlier that glucose entered pancreatic beta cells through GLUT2 transporters.) These transporters differ in their location, sensitivity to hormones, and specificity (some are more specific for transporting other monosaccharides, such as fructose, than for transporting glucose). Only one of these transporters, GLUT4, is sensitive to insulin. GLUT4 is a facilitated diffusion transporter for glucose and is the most important glucose transporter for whole-body metabolism. Skeletal muscle and adipose tissue cells have pools of GLUT4 transporters that are stored in vesicles in the cytoplasm. Insulin can either trigger insertion of these stored transporters into the plasma membrane by exocytosis or stimulate the synthesis of new transporters. Exercise also triggers expression of GLUT4 on the plasma membrane of skeletal muscle cells and adipocytes.

The transport of glucose in the central nervous system and the liver is not affected by insulin. The isolation of this process is critical, because when insulin levels are low during the postabsorptive state, glucose uptake by most cells is decreased, sparing the glucose for use by cells of the central nervous system, where glucose transport is not affected by insulin. In addition, during the postabsorptive state, the liver produces glucose that must be transported into the blood.

In addition to the actions shown in Figure 21.5, insulin has important growth-promoting effects. Although insulin by itself does not stimulate growth, it must be present in the blood for growth hormone to exert its normal effects, a form of permissiveness (discussed in Chapter 6). This need results, at least in part, from insulin’s role in promoting protein synthesis, DNA synthesis, and cell division, all of which are essential to tissue growth.

The Role of Glucagon

Insulin’s actions to bring about the body’s metabolic adaptations to the absorptive and postabsorptive states are reinforced by contrary changes in glucagon, a peptide hormone secreted by alpha cells of pancreatic islets of Langerhans. Put another way, insulin and glucagon are antagonists, hormones whose actions oppose each other. Insulin promotes processes of the absorptive state; glucagon promotes processes of the postabsorptive state.

Glucagon secretion decreases during the absorptive state and increases during the postabsorptive state. Because insulin levels are also changing with these states, the metabolic adjustments from one state to the other are orchestrated by contrary changes in plasma levels of insulin and glucagon.

Factors Affecting Glucagon Secretion

Most of the signals that stimulate the secretion of glucagon are the same signals that inhibit the secretion of insulin (see Table 21.3). For instance, decreases in blood glucose both stimulate glucagon secretion and inhibit insulin secretion. Likewise, glucagon secretion is stimulated by sympathetic nervous activity and epinephrine, which have a suppressive effect on insulin secretion. Some studies suggest that glucagon and insulin function as paracrine hormones, with a suppressive effect on insulin secretion. Because of the opposite controls of these hormones, plasma glucagon levels tend to rise as insulin levels fall, and vice versa.

Actions of Glucagon

Figure 21.7 shows that the actions of glucagon, though more limited than those of insulin, oppose insulin’s actions. In the liver, glucagon promotes glycogenolysis and gluconeogenesis (which increase blood glucose levels), ketone synthesis, and breakdown of proteins, while inhibiting the opposing processes of glycogen and protein synthesis. In adipose tissue, glucagon stimulates lipolysis and suppresses triglyceride synthesis. These actions lead to glucagon’s classification as a catabolic hormone. The overall effect of glucagon promotes mobilization of energy stores and synthesis of “new” energy sources (glucose and ketone bodies) that can be used by tissues; all of these actions are characteristic of the postabsorptive state.

Negative Feedback Control of Blood Glucose Levels by Insulin and Glucagon

Plasma glucose levels are normally tightly regulated by the antagonistic actions of insulin and glucagon to maintain stability. (Other hormones, described below, also regulate plasma glucose levels.) This stability is important because deviations too far from normal in either direction can have serious adverse effects on health. The normal fasting level of glucose in the blood is 70–110 mg/dL (clinical measures usually assess blood—not plasma—glucose levels). Fasting blood glucose levels greater than 140 mg/dL constitute hyperglycemia, which is often indicative of diabetes mellitus, a serious and increasingly common
disease involving defects in insulin production or signaling. Fasting blood glucose levels below 60 mg/dL constitute hypoglycemia, which has widespread deleterious effects on nervous system function because the nervous system uses glucose almost exclusively as its source of energy.

Insulin and glucagon together control plasma glucose concentration through negative feedback (Figure 21.8). An increase in plasma glucose concentration increases insulin secretion and decreases glucagon secretion from the pancreas, both of which cause a decrease in plasma glucose. Similarly, a decrease in plasma glucose concentration decreases insulin secretion and increases glucagon secretion, both of which cause an increase in plasma glucose.

Figure 21.8a diagrams insulin’s negative feedback control of plasma glucose concentration. An increase in plasma glucose stimulates insulin secretion from pancreatic beta cells, and the actions of insulin decrease plasma glucose. Insulin decreases plasma glucose concentration in three ways: (1) by promoting the uptake of glucose into cells by increasing the expression of GLUT4 transporters in the plasma membrane; (2) by reducing the concentration of free glucose within cells by converting it to glycogen, which promotes glucose uptake by increasing the size of the glucose concentration gradient; and (3) by suppressing gluconeogenesis, thereby reducing the rate at which new glucose is released into the bloodstream. If plasma glucose concentration decreases, insulin secretion decreases, causing an increase in plasma glucose.

Figure 21.8b illustrates glucagon’s negative feedback control of plasma glucose concentration. A decrease in plasma glucose stimulates glucagon secretion from alpha cells of the pancreas, and the actions of glucagon increase plasma glucose. Glucagon increases plasma glucose concentration by promoting gluconeogenesis and glycogenolysis in the liver, which directly increases plasma glucose concentration, and by stimulating lipolysis in adipose tissue, which provides fatty acids as an alternate energy source to glucose.

### Stimulation of Insulin and Glucagon Secretion by Amino Acids

Although insulin secretion and glucagon secretion are usually affected in opposite ways by a given stimulus, some exceptions to this pattern have been noted (see Table 21.3). For example, an increase in plasma amino acids stimulates the release of both insulin and glucagon (see Figures 7.7 and 7.8). Although this effect might seem counterproductive, it is not. Consider what happens following a person’s consumption of a meal rich in proteins but low in carbohydrates: When the nutrients are absorbed, plasma amino acid levels rise significantly, but glucose levels either do not change or rise only slightly. The rise in amino acids stimulates insulin secretion, which promotes increases in amino acid uptake by cells. At the same time, the rise in insulin tends to promote a decrease in plasma glucose. Because the plasma glucose level was already near normal, this change is inappropriate and potentially dangerous. However, the rise in plasma amino acids also stimulates the secretion of glucagon, which promotes increases in amino acid uptake by cells. At the same time, the rise in insulin tends to promote a decrease in plasma glucose. Because the plasma glucose level was already near normal, this change is inappropriate and potentially dangerous.

Figure 21.8a illustrates insulin’s negative feedback control of plasma glucose concentration. An increase in plasma glucose stimulates insulin secretion from pancreatic beta cells, and the actions of insulin decrease plasma glucose. Insulin decreases plasma glucose concentration in three ways: (1) by promoting the uptake of glucose into cells by increasing the expression of GLUT4 transporters in the plasma membrane; (2) by reducing the concentration of free glucose within cells by converting it to glycogen, which promotes glucose uptake by increasing the size of the glucose concentration gradient; and (3) by suppressing gluconeogenesis, thereby reducing the rate at which new glucose is released into the bloodstream. If plasma glucose concentration decreases, insulin secretion decreases, causing an increase in plasma glucose.

Figure 21.8b illustrates glucagon’s negative feedback control of plasma glucose concentration. A decrease in plasma glucose stimulates glucagon secretion from alpha cells of the pancreas, and the actions of glucagon increase plasma glucose. Glucagon increases plasma glucose concentration by promoting gluconeogenesis and glycogenolysis in the liver, which directly increases plasma glucose concentration, and by stimulating lipolysis in adipose tissue, which provides fatty acids as an alternate energy source to glucose.

**Figure 21.8** Regulation of plasma glucose concentration. (a) Negative feedback control of plasma glucose by insulin. (b) Negative feedback control of plasma glucose by glucagon.
Effects of Epinephrine and Sympathetic Nervous Activity on Metabolism

Table 21.3 indicates that the sympathetic nervous system and epinephrine suppress insulin secretion and stimulate glucagon secretion, thereby indirectly promoting metabolic adjustments to the postabsorptive state. Sympathetic neurons and epinephrine also directly affect metabolism of certain target tissues.

The postabsorptive period is characterized by decreased plasma glucose levels, which act directly on alpha and beta pancreatic cells to increase glucagon secretion and decrease insulin secretion, respectively. In similar fashion, a decrease in plasma glucose acts directly on glucose receptors in the central nervous system to raise the level of activity in sympathetic neurons, which triggers a rise in epinephrine secretion by the adrenal medulla; the resulting increase in plasma epinephrine acts on the liver to increase glycogenolysis and gluconeogenesis, on skeletal muscle to increase glycolysis, and on adipose tissue to increase lipolysis. Similar actions are promoted by sympathetic neural input to the liver and adipose tissue. (Skeletal muscle cells do not receive input from sympathetic neurons.)

Although sympathetic control of metabolism plays a role in adapting the body to the postabsorptive state, under normal circumstances its influence is relatively minor compared to that of insulin and glucagon. The major importance of the sympathetic influence on metabolism becomes apparent in the body's reaction to stress—a general term for any condition that actually or potentially poses a serious challenge to the body's ability to maintain homeostasis. (Stress includes both physical conditions, such as dehydration, hemorrhage, infection, exposure to temperature extremes, trauma, or severe exercise, and psychological states, such as pain, fear, or anxiety.) Activation of the sympathetic nervous system by stressors (things that cause stress) triggers the familiar constellation of fight-or-flight responses (accelerated heart rate, generalized vasoconstriction, dilation of respiratory airways, and generalized vasoconstriction, dilation of respiratory airways, and
so on); it also elevates plasma glucose levels (due to increased gluconeogenesis and glycogenolysis in the liver) and plasma levels of fatty acids and glycerol (due to increased lipolysis in adipocytes). These actions make fuel more readily available to cells, in the process helping prepare the body for the strenuous physical activity inherent in the fight-or-flight response. The increased availability of fuel also prepares the body for other activities requiring energy, such as tissue repair or fighting infections. Other components of the body’s response to stress are described later in this chapter.

Clearly, whole-body metabolism is highly regulated, for important reasons. Notably, diseases of body metabolism affect all organ systems, as is most apparent in diabetes mellitus (see Focus on Diabetes: Diabetes Mellitus, page 615).

Quick Check 21.3

1. The concentration of which hormone, insulin or glucagon, is increased during the absorptive period?
2. Sympathetic nervous activity and epinephrine promote metabolic reactions characteristic of which state, the absorptive state or the postabsorptive state?
3. For each of the following processes, indicate whether it is promoted by insulin or by glucagon: gluconeogenesis, glucose uptake by cells, glycogenolysis, glycogen synthesis, catabolism of energy stores, protein synthesis, a decrease in blood glucose levels, triglyceride synthesis, lipolysis.

21.6 Thermoregulation

When nighttime comes to the desert, the snakes, lizards, and insects that were active in the noonday sun begin to sink into a state of relative torpor; many are barely able to move at all. This change occurs because the falling temperature causes these animals’ bodies to cool, which slows down biochemical reactions and other metabolic processes. By contrast, humans and other mammals are less affected by changes in the ambient temperature because they have the ability to maintain their body temperatures within a fairly narrow range through thermoregulation. Animals with this ability are said to be homeothermic, whereas those lacking this ability are called poikilothermic.

Temperature Balance

All living things produce heat as a by-product of metabolism, but humans (like all other homeothermic animals) are able to control body temperature by regulating the rates at which heat is produced and lost from their bodies. To maintain a normal body temperature, the rate of heat production must be balanced against the rate of heat loss. In negative heat balance, heat loss exceeds heat produced; as a result, body temperature falls below normal, a condition called hypothermia. People who are trapped in snowstorms or swept from a boat into icy waters, for example, are vulnerable to hypothermia. Such misfortunes can quickly lead to stupor, loss of consciousness, multiple-organ failure, and ultimately death. In positive heat balance, heat produced exceeds heat loss and body temperature increases to levels above normal; this condition, called hyperthermia, can lead to loss of consciousness, convulsions, respiratory failure, and death. Adverse effects begin to appear when body temperature approaches 41°C (106°F); a temperature of 43°C (109°F) or higher is usually fatal (see Chapter 1, Clinical Connections: Heat Exhaustion and Heat Stroke, p. 10). The ability to maintain normal body temperature depends on the adequacy of heat transfer with the environment.

Mechanisms of Heat Transfer

Between the Body and the External Environment

Under most conditions, the body loses heat to the environment because the surrounding temperature is often lower than body temperature. When the rate of heat loss equals the rate of heat generation, body temperature does not change. Generally speaking, heat is lost by four mechanisms: (1) radiation, (2) conduction, (3) evaporation, and (4) convection.

In radiation, thermal energy is transferred from the body to the environment in the form of electromagnetic waves. A general law of physics states that all objects emit and absorb these waves, albeit to varying degrees. When an object is warmer than its surroundings, it loses heat by emitting more energy than it absorbs. For example, when you are outside in the cool fall air, you emit radiant energy to the air molecules around you, making your body colder. By contrast, if an object is cooler than its surroundings, it gains heat by absorbing more energy than it emits. For example, if you are sitting by a campfire, your body absorbs radiant heat and becomes warmer.

Conduction is the transfer of thermal energy between objects that are in direct contact with each other. As in radiation, heat is always transferred from the warmer object to the cooler object. When you touch cold metal, for example, you feel colder because thermal energy is transferred directly from your skin to the metal.

In evaporation, heat is lost from an object through the evaporation of water from its surface. For water to evaporate from your body, the water must be converted from liquid form to gaseous form, a process that requires thermal energy obtained from the body. Water evaporates from the skin, the lining of the airways, and other moist surfaces such as the lining of the mouth. This kind of insensible water loss occurs continually without your being aware of it (hence the name). Your body also loses water through the evaporation of sweat, a salt-containing solution secreted by numerous small sweat glands in the skin. Unlike insensible water loss, which occurs continuously, sweat production is regulated according to the body’s needs. When increased heat loss is desirable, sweat production increases. As a result, more water evaporates from the skin surface, carrying thermal energy away from the body.

When the environmental temperature is warmer than the body temperature, radiation and conduction transfer heat into the body. This transfer adds to the heat generated by the body itself, boosting the need for heat loss. During such circumstances, the body must rely on evaporation to carry heat away by increasing the production of sweat. Sweating cools the body under these conditions because water continues to evaporate even when it is cooler than its surroundings, assuming that the humidity of the surroundings is not too high. In a humid environment, sweating is not as efficient as in drier air because water cannot evaporate into already
Convection—the transfer of heat from one place to another by a moving gas or liquid—contributes to heat loss on a windy day. On a still day, the air that is closer to your skin warms up as it absorbs heat from your body’s surface. This warmer air forms a kind of “blanket” around you that slows down the rate of heat loss by conduction. Because the air in this protective layer contains moisture that has evaporated from your skin, it tends to have a higher humidity than the surrounding air. The presence of this moisture near the skin reduces the rate of evaporative heat loss. In contrast, when the surrounding air is moving, as on a windy day, the thickness of the protective “blanket” of air is reduced, and conductive and evaporative heat loss both increase. Thus convection is responsible for the wind chill factor reported by meteorologists on cold, windy days.

Regulation of Body Temperature

The body’s thermoregulatory efforts maintain the core temperature, the temperature within internal structures, including those of the central nervous system and abdominal and thoracic cavities (Figure 21.9). This temperature is normally regulated at approximately 37°C (98.6°F). Within the hypothalamus is the body’s thermoregulatory center, which contains both heat-losing and heat-promoting centers. Input about the core temperature is transmitted to the thermoregulatory center from central thermoreceptors that include temperature-sensitive neurons within this region of the brain, in other areas of the central nervous system, and in other internal organs. Input of changes in core temperature is necessary to initiate the thermoregulatory responses that return the core temperature to normal. Other thermoreceptors, called peripheral thermoreceptors, are located in the skin; they detect the temperature of the skin, which is usually well below the core temperature and is more variable. Our bodies do not regulate skin temperature, but information about skin temperature enables us to compensate for changes in environmental temperatures by making behavioral adjustments, such as dressing appropriately or avoiding extreme temperatures altogether.

Thermoregulation in the Thermoneutral Zone

The primary mechanism for regulating body temperature is to vary the amount of blood flowing to the skin, where thermal energy in the blood can be exchanged with that in the environment (the heat actually moves from blood to cutaneous tissue and then out of the body). When body temperature decreases, blood flow to the skin decreases, so that the blood loses less of its heat to the environment. Likewise, when body temperature increases, blood flow to the skin increases, so that the blood can lose more of its heat to the environment. Alterations in blood flow to the skin are sufficient to maintain body temperature when the environmental temperature is maintained within a narrow range called the thermoneutral zone (25–30°C).

The sympathetic nervous system regulates cutaneous blood flow based on input from the thermoregulatory center. As we learned earlier (in Chapter 14), arteriole radius is regulated by sympathetic activity, with increases in sympathetic activity causing vasoconstriction. The arterioles to skin follow this same rule. Thus, when body temperature decreases, sympathetic activity to the arterioles increases, causing vasoconstriction and thereby decreasing cutaneous blood flow to conserve body heat. In contrast, when body temperature increases, sympathetic activity decreases, causing vasodilation and an increase in blood flow to the skin, thereby transferring heat to the environment. When the environmental temperature is outside the thermoneutral zone, other thermoregulatory mechanisms must be activated to maintain body temperature.

Heat Generation in a Cold Environment

When the environmental temperature drops to less than 25°C, decrease in cutaneous blood flow alone cannot prevent body temperature from falling. In this circumstance, the heat-promoting center of the hypothalamus communicates to effector organs to stimulate shivering and decrease sweat production (Figure 21.10).

Shivering is the primary mechanism by which our bodies can increase heat production for the purpose of increasing body temperature, a process called shivering thermogenesis. Shivering involves the rapid rhythmic contraction of skeletal muscles and is controlled by a spinal reflex. As the muscles contract, they generate heat. Human infants and hibernating mammals are also capable of generating heat through non-shivering thermogenesis. Infants have a special form of adipose tissue, called brown adipose tissue, that generates heat through the uncoupling of the electron
transport chain from oxidative phosphorylation. Thus the energy released by electrons is “lost” as heat instead of being harnessed to synthesize ATP. By comparison, adult humans have little, if any, brown adipose tissue.

**Heat Loss in a Warm Environment**

When environmental temperature increases above the thermoneutral zone, the body must respond with more than cutaneous vasodilation if it is to remove enough heat to bring body temperature back toward normal. Specifically, the body produces sweat for evaporative heat loss.

The average person has approximately 2.5 million sweat glands located in skin throughout the body, except in the lips, nipples, and external genitalia. Two types of sweat glands are distinguished: (1) **eccrine glands** (the more common), which are located all over the body but especially in the forehead, palms of the hands, and soles of the feet, and (2) **apocrine glands**, which are located primarily in the axillary region (arm pits) and the anal-genital region. Eccrine glands empty into pores at the surface of the skin, whereas apocrine glands empty into hair follicles. Eccrine glands are active at birth, but apocrine glands do not become active until puberty. The amount of sweat produced by both types of glands depends on the body temperature and level of sympathetic activity.

Eccrine sweat glands produce a primary secretion of water, sodium, and chloride, plus a trace amount of potassium (Figure 21.11). As this fluid makes its way through the duct leading to the skin surface, the sodium and chloride are actively reabsorbed, and water follows the same path by osmosis. However, the quantity of water and electrolytes reabsorbed depends on the rate of sweat production; as the rate increases, less is reabsorbed and more is secreted outside the body. The sympathetic nervous system controls the rate of sweat production; as sympathetic activity increases (whether due to a warm environment or activation of the fight-or-flight response), sweat production increases. Sympathetic innervation of sweat glands is atypical, in that the sympathetic postganglionic neurons secrete acetylcholine instead of norepinephrine.

Apocrine sweat glands produce sweat in a similar manner, but proteins and fatty acids are also found in the sweat produced via this mechanism. Proteins and fatty acids secreted on the skin surface provide nutrition that allows bacteria to grow. As the bacteria grow, they generate waste products that create the odor associated with sweat in the axillary and genital areas.

**Alterations in the Set Point for Thermoregulation: Fever**

During an infection, certain white blood cells produce cytokines that function as **pyrogens**, chemicals that induce fever. A normal response of the immune system (described in Chapter 23), this effect promotes several immune responses that fight the infection. Thus fever is actually considered beneficial because it enhances the body’s ability to defend itself.

Pyrogens induce a fever through actions on the thermoregulatory center, adjusting the temperature to be maintained by thermoregulatory processes to a higher level. The body responds by
increasing heat production and minimizing heat loss. As a result, a person with an infection tends to appear white (due to decreased blood flow to the skin) and to shiver. The person may also feel cold even though he or she is warm because of the contradictory neural signals sent during this situation.

21.7 Hormonal Regulation of Growth

Although feeding (or the lack of it) is certainly a significant factor in the regulation of the body’s overall metabolism, it is not the only one. In this section we explore the actions of hormones that play little (if any) role in everyday adjustments to feeding and fasting but nevertheless exert important influences on energy metabolism as they promote growth.

Body Growth

During their first two years of life, humans experience a dramatic increase in height and body weight, a phenomenon called the postnatal growth spurt (Figure 21.12). After age 2 years, growth continues at a slower rate until the beginning of adolescence (about age 11 years for girls and age 13 years for boys), at which time another period of rapid growth, known as the pubertal growth spurt, begins. At the end of adolescence, which occurs in the late teens, growth stops, and individuals attain their full adult stature. Thereafter, no further increase in height is possible, although obviously a person’s weight may increase. Unless otherwise noted, in this text the term growth refers to the bodily changes that normally accompany increases in height only.

During periods of growth, both the size and number of cells in the body’s soft tissues (nonbony tissues such as skin and muscle) increase, as does the length and thickness of bones. Observed increases in height are mostly attributable to increases in the length of bones in the legs and vertebral column. Lengthening of long bones in the limbs (the femur of the thigh or the humerus of the arm, for instance) is largely responsible for the changes in body proportion that accompany growth.

Body growth during childhood is regulated primarily by hormones, but it is also influenced by a person’s genetic makeup, diet, and other factors such as disease or stress. Many of the bodily changes occurring during growth are attributable to the actions of growth hormone (GH), a peptide hormone secreted by the anterior pituitary (see Chapter 6). Other hormones that are essential for normal growth include insulin, the thyroid hormones, and the sex hormones (androgens and estrogens), which are especially important during the pubertal growth spurt. In addition, growth of various organs and tissues is influenced by numerous growth factors and growth-inhibiting factors that are usually specific to certain types of tissues and act locally as paracrine or autocrine agents. Nerve growth factor, for example, promotes elongation and proliferation of the axons and dendrites of neurons.

In the following subsection, we concentrate on the actions of growth hormone and the factors influencing its secretion; the influence of other hormones on growth is discussed shortly.
Effects of Growth Hormone

In children, GH exerts several effects on bones and soft tissues that result in body growth. In adults, it demonstrates many of the same effects, but instead of promoting growth it maintains bone mass and lean body mass, which is the proportion of body weight that is contributed by muscle (as opposed to fat).

Growth hormone directly promotes growth in two ways: It stimulates protein synthesis, thereby increasing cell size (hypertrophy), and it stimulates cell division, which results in increased cell number (hyperplasia). The results of these actions are linear growth (increased height) due to the elongation of bones, an increase in lean body mass due to the growth of muscle tissue, and an increase in the size of individual organs, including the heart, lungs, kidneys, and intestines.

Growth hormone also indirectly promotes a number of actions that affect growth (Figure 21.13). GH increases the plasma concentrations of glucose, fatty acids, and glycerol by inhibiting glucose uptake in adipose tissue and skeletal muscle, by stimulating lipolysis in adipose tissue, and by stimulating gluconeogenesis in the liver. Increasing plasma levels of these nutrients make energy more readily available to tissues, which must expend energy to grow. GH also promotes increased uptake of amino acids by cells in muscle and other tissues, which facilitates protein synthesis.

Growth hormone alone cannot ensure normal growth; an adequate diet is clearly essential in providing the raw materials for growth. During growth, increases in the body’s total protein mass resulting from protein synthesis require an abundant supply of amino acids, which are most easily provided by eating protein-rich foods. Certain amino acids can be synthesized if they are lacking in the diet, but essential amino acids must be consumed in the diet. Many other raw materials for tissue growth, such as calcium for bones, must also be present in the diet in sufficient quantity. Finally, the energy content of the diet must provide enough calories to meet the heightened energy demands of growth. If the diet is inadequate in any of these respects, growth is inhibited. In younger children especially, the growth-stunting effects of poor diet are often irreversible.

Many of the growth-promoting effects of GH result from the actions of intermediary chemical messengers on target tissues, rather than a direct action of GH itself. These messengers are peptides known as insulin-like growth factors (IGFs) because they bear some structural resemblance to insulin. To date, two IGFs (IGF-1 and IGF-2) have been positively identified. IGF-2 is important during gestational growth, whereas IGF-1 plays a role in growth following birth. GH stimulates the production of IGFs by the liver, which secretes these molecules into the bloodstream for transport to target tissues throughout the body. In this respect, IGFs function as hormones. GH also stimulates the production of IGFs in other target tissues, where they act locally as paracines.

![Figure 21.13](image_url) Growth hormone secretion and actions on target tissues.
Factors Affecting Growth Hormone Secretion

Secretion of GH by the anterior pituitary is regulated by two hypothalamic hormones: growth hormone releasing hormone (GHRH), which stimulates GH secretion, and growth hormone inhibiting hormone (GHIH; also known as somatostatin), which inhibits GH secretion (see Figure 21.13). Although the relative importance of these two hormones is unclear, variations in GH secretion are likely triggered primarily by GHRH, with GHIH playing a relatively minor role. As is true with other anterior pituitary hormones, GH secretion is regulated through negative feedback loops (see Chapter 6). GH limits its own secretion via short loop negative feedback on the hypothalamus. Plasma IGFs also exert long loop negative feedback controls on the hypothalamus and anterior pituitary to inhibit GHRH and GH secretion, respectively.

GHRH secretion is regulated by neural input of various types to the hypothalamus. Secretion is affected by plasma nutrient concentrations; specifically, decreases in plasma glucose or fatty acid levels, or increases in plasma amino acid levels, stimulate GHRH secretion. Because it promotes changes in the opposite direction (by reducing glucose uptake and increasing lipolysis and amino acid uptake), GH acts by negative feedback to limit variations in these nutrient concentrations in plasma. GH secretion is also stimulated in response to exercise, stress, or sleep. A boost in GH during exercise or stress is useful because it tends to counteract reduced plasma levels of glucose and fatty acids, thereby helping to maintain a steady supply of these much-needed energy sources. The significance of heightened GH secretion during sleep is not understood. GH secretion is also subject to a circadian rhythm that is mediated by neural input to the hypothalamus, with GH levels increasing at night and decreasing by day. (Secretion reaches its peak about 1-2 hours after the onset of sleep.)

Average daily plasma levels of GH also vary with a person’s age. These levels generally reach a maximum during puberty, but then decline with age. Decreased GH levels are thought to be at least partially responsible for some signs of aging, such as decreased muscle mass and increased body fat.

Bone Growth

Because stimulation of bone growth is an important part of growth hormone’s actions, it is appropriate to consider the nature of bone in some detail here. Bone is also an important reserve for calcium, which can be liberated and moved into the bloodstream when plasma calcium levels decrease.

To support the weight of the body and to withstand the forces placed on it by contracting muscles, bone must be strong but not brittle. Crystals of calcium phosphate in a form known as hydroxyapatite \( \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 \) give bone a mineral component that helps it withstand compressive forces (that is, “squeezing” or “crushing” forces). Osteoid, an organic component that consists of collagen fibers embedded in a gel-like substance, gives bone its ability to withstand tensile or stretching forces, making it less prone to fracture.

Despite its nonliving organic and mineral components, bone is a dynamic living tissue that contains cells. The dynamic nature of bone is evident not only in its ability to grow during childhood but also in the fact that bone can heal following a fracture and adapt its structure in response to forces placed on it. In a person who engages regularly in heavy lifting, for instance, the weight-bearing bones gradually increase in thickness and strength. In a person who is sedentary or bedridden, bone mass diminishes over time. Such restructuring of bone is called remodeling, and it is critical to the body’s ability to regulate plasma calcium levels.

Central to the remodeling of bone are mobile cells known as osteoblasts and osteoclasts, both of which are found on the outer surfaces and inner cavities of bone tissue (Figure 21.14). Osteoblasts, or “bone makers,” are responsible for building up the mass of bone tissue, a process called deposition. Osteoclasts, or “bone breakers,” are responsible for breaking down bone tissue, a process called resorption. When the activity of osteoblasts exceeds that of osteoclasts—that is, when deposition exceeds resorption—bone growth occurs.

Osteoblasts initiate bone deposition by laying down the osteoid, which is followed by deposition of calcium phosphate, a process called calcification. The mechanism of calcification, which takes several days, is poorly understood, but it seems that intracellular calcium is attracted to the osteoid and calcifies it. As an osteoblast works to build bone, it eventually becomes immobilized within the surrounding tissue and is transformed into an osteocyte, another type of cell that maintains the surrounding matrix but no longer actively lays down new bone tissue. An osteocyte is distinguishable from other bone cells in that it possesses long, filamentous processes that extend through channels in the bone tissue called canaliculi. These cell processes come into contact with processes belonging to other osteocytes or with nearby osteoblasts, such that the cells can communicate with one another through gap junctions. This communication is important because it allows cells in the interior of the bone tissue to exchange nutrients, wastes, and other materials with blood vessels, which run through bone cavities.

Osteoclasts affect resorption of bone tissue by secreting both acid that dissolves calcium phosphate crystals, and enzymes that break down osteoid. Resorption releases calcium and phosphate into the bloodstream. Recall (from Chapter 19) that bone deposition and resorption are also important for calcium balance.

Apply Your Knowledge

Rickets is a disease, primarily affecting children, in which the bones are weak because of a deficiency in vitamin D, calcium, or phosphate. Explain how each of these deficiencies can result in weak bones.

Bone deposition is also necessary for increases in height, which occur through the growth of long bones. Figure 21.15 shows the structure of a typical long bone, which consists of a long, nearly cylindrical shaft capped at either end by a knob called an epiphysis. In the bones of growing children, the epiphyses are separated from the shaft by a thin layer of tissue called the epiphyseal plate, which is composed of cartilage, a soft material similar to uncalcified osteoid. The epiphyseal plate plays a key role in the elongation of bones during growth. Inside most bones is a central cavity containing red
outer bone surfaces. This process is accompanied by resorption of bone by osteoclasts at the inner surface of the marrow cavity. As a consequence, the diameter of the marrow cavity increases as the outer diameter of the bone increases, which minimizes weight gain while increasing strength.

Increases in the length of a bone result from the addition of new bone tissue to either end of the bone shaft (Figure 21.16). This process begins with the activity of cells in the epiphyseal plate called chondrocytes, which are similar to osteoblasts except that they produce cartilage rather than bone. Under the influence of GH, chondrocytes increase in size and number, forming a layer of cartilage that causes the epiphyseal plate to become wider (elongating the bone). As new cartilage forms, chondrocytes located in the region adjacent to the shaft die, and osteoblasts from the nearby bone tissue replace them and begin converting the cartilage to bone. In this manner, new bone is added to the end of the bone shaft.

In late adolescence, the epiphyseal plates become completely filled in with bone tissue, a process called epiphyseal plate closure. When closure is complete, GH can no longer stimulate bone elongation, and bones stop lengthening. This is why further increases in height are generally not possible after adolescence (even though changes in bone circumference and remodeling of bone continue). Plate closure is influenced by sex hormones—that is, androgens and estrogens—during puberty.

---

**Figure 21.14** The structure of bone.

**Q** Which type of cell breaks down bone?

Bone marrow and yellow bone marrow. Red bone marrow produces red and white blood cells; yellow bone marrow contains primarily adipocytes.

Under the influence of GH, bones increase in both circumference and length. The increase in circumference is brought about through the action of osteoblasts, which lay down new tissue on the

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**Figure 21.15** Structure of a long bone (the femur).
Sex hormone levels remain low until a few years before puberty and play little (if any) role in early childhood growth. In puberty, however, the dramatic increase in sex hormone secretion is essential for the growth spurt that normally occurs during this period. In contrast to insulin and the thyroid hormones, which are permissive for growth, the sex hormones actively promote growth by stimulating the secretion of GH and IGF-1. In addition, the sex hormones stop bone elongation by virtue of their role in promoting epiphyseal plate closure. Androgens (testosterone in men and adrenal androgens in women) exert an additional growth-promoting effect by directly stimulating protein synthesis in many tissues, including skeletal muscle. The marked rise in muscle mass that occurs in boys during puberty is largely due to the increased testosterone levels observed during this period.

In contrast to the growth-promoting hormones mentioned so far, high concentrations of the glucocorticoids (such as cortisol) secreted from the adrenal cortex inhibit growth, in part because they promote bone resorption and protein catabolism. It is also worth noting that glucocorticoid secretion is stimulated by stress, which is one possible explanation for the observation that illness and other forms of stress can have a growth-retarding effect. Glucocorticoids and their role in stress are described later in this chapter.

**Effects of Abnormal Growth**

**Hormone Secretion**

Deficient GH secretion during childhood leads to a condition known as dwarfism, an irreversible stunting of growth, poor muscle development, and higher-than-normal amounts of body fat. Dwarfism is sometimes also caused by deficient tissue responsiveness to GH, which can result from defective GH receptors, insufficient production of IGFs, or failure of tissues to respond to IGFs. Abnormally low GH secretion in adults produces few noticeable signs other than decreased muscle or bone mass.

When excessive secretion of GH occurs before closure of the epiphyseal plates, the result can be gigantism, a condition in which stature is abnormally large but the body is normally proportioned (see Chapter 6, *Clinical Connections: Pituitary Adenomas*, p. 163, for an example of gigantism). An excess of GH that occurs following plate closure results in acromegaly. In this syndrome, no change in height occurs, but the overgrowth of soft tissues and an increase in bone circumference produce a characteristic pattern of disfiguration in certain body parts. Individuals with untreated acromegaly typically have an overly wide, protruding jaw (sometimes referred to as a "lantern jaw") and overly long limbs.

**Other Hormones That Affect Growth**

Normal body growth requires the actions of other hormones besides GH, including thyroid hormones, sex hormones, and insulin. Thyroid hormones are required for the synthesis of GH and are generally permissive for its actions; that is, thyroid hormones are required for GH to exert its effects on target tissues. (Other actions of thyroid hormones are described later in this chapter.) Insulin is also permissive for growth because it is required for secretion of IGF-1 and for normal protein synthesis in general.

Sex hormone levels remain low until a few years before puberty and play little (if any) role in early childhood growth. In puberty, however, the dramatic increase in sex hormone secretion is essential for the growth spurt that normally occurs during this period. In contrast to insulin and the thyroid hormones, which are permissive for growth, the sex hormones actively promote growth by stimulating the secretion of GH and IGF-1. In addition, the sex hormones stop bone elongation by virtue of their role in promoting epiphyseal plate closure. Androgens (testosterone in men and adrenal androgens in women) exert an additional growth-promoting effect by directly stimulating protein synthesis in many tissues, including skeletal muscle. The marked rise in muscle mass that occurs in boys during puberty is largely due to the increased testosterone levels observed during this period.

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**Quick Check 21.4**

1. Describe the roles of osteoblasts, osteoclasts, and osteocytes in bone remodeling.
2. What are IGFs? What is their role with respect to body growth?
3. Why are further increases in body height not possible after adolescence?
21.8 Thyroid Hormones

Unlike the hormones we have studied so far, which show large changes in their rates of secretion throughout the course of a normal day, the thyroid hormones show little variation and their plasma levels hold nearly steady. Consequently, the thyroid hormones do not normally "trigger" effects; instead, they simply work to maintain the status quo.

Synthesis and Secretion of Thyroid Hormones

The thyroid gland contains numerous follicles that produce the thyroid hormones (TH; Figure 21.17a). Each follicle consists of a single outer layer of follicular cells surrounding a central protein-rich colloid secreted by the follicular cells. Located in the interstitial space between the follicles are C cells, which synthesize and secrete calcitonin (see Chapter 19). This section discusses the synthesis and secretion of thyroid hormones.

Thyroglobulin (TG), the primary protein found in the colloid, is the precursor molecule for TH. Also located in the colloid are the enzymes required for TH synthesis and iodide (ionized form of iodine, \( I^- \)). The thyroglobulin and enzymes are synthesized in the follicular cells and secreted into the colloid by exocytosis; the iodide is actively transported by follicular cells from the blood into the colloid and is a necessary component of TH. Thus all components of TH synthesis are located in the colloid.

The steps of TH synthesis and secretion proceed as follows (Figure 21.17b):

1. Tyrosine residues of TG are iodinated. Addition of one iodide forms monoiotyrosine (MIT), whereas addition of a second iodide to the same tyrosine residue forms diiodotyrosine (DIT).

2. Two iodinated tyrosine residues (MIT or DIT) on the same TG molecule are coupled, meaning that the two tyrosine residues are linked together by a covalent bond. If two DIT groups combine, the final product is 3,5, 3',5'-triiodothyronine or T3 (also called thyroxine); if a DIT and an MIT combine, the final product is 3, 3'-triiodothyronine or T2. T3 and T4 are the thyroid hormones, although at this step they are still attached to TG. Note that two MIT groups cannot combine.

3. Thyroid hormones are stored in the colloid bound to TG for up to three months.

4. Thyroid stimulating hormone (TSH) arriving via the bloodstream binds to receptors on the membrane of follicular cells, activating the cAMP second messenger system. The result is phosphorylation of a variety of follicular cell proteins necessary for the release of thyroid hormones.

5. The follicular cells take in iodinated TG molecules from the colloid by phagocytosis.

6. The phagosome containing the iodinated TG fuses with a lysosome.

7. Exposure of the TG molecule to lysosomal enzymes that break down the thyroglobulin triggers the release of free T3 and T4 into the follicular cell. Because T3 and T4 are lipophilic, they can diffuse across the plasma membrane and into the bloodstream, where they are selectively bound by protein carriers that include thyroxine-binding globulin and transthyretin, and nonselectively bound by albumin.

T4 is normally produced and secreted at a rate approximately 10 times greater than the rate for T3. However, T3 is approximately 4 times more potent at the target tissues. Most of the T4 that is secreted into the plasma is eventually converted by the liver,
thyroid hormones, or target tissues to the more active form, $T_3$; in fact, the majority of $T_4$ in the plasma is synthesized from circulating $T_4$. Conversion of $T_4$ to $T_3$ is called activation.

TH levels remain virtually constant under normal conditions because the primary control of this hormone’s secretion occurs via negative feedback. As we have seen, TH secretion is stimulated by TSH from the anterior pituitary. Secretion of TSH is, in turn, stimulated by thyrotropin releasing hormone (TRH) from the hypothalamus. Once released into the bloodstream, TH feeds back to the hypothalamus and the anterior pituitary to limit the secretion of TRH and TSH. Interestingly, $T_4$ provides stronger negative feedback than $T_3$.

The only known stimulus for TRH secretion, and thus for TH secretion, is exposure to cold temperatures. This action is more pronounced in infants than in older children and is virtually absent in adults. In infants, the cold-stimulated TRH secretion is thought to promote heat production as the infant adapts to a colder environment outside the mother’s body. TRH secretion, and thus TH secretion, is inhibited by stress through neural input to the hypothalamus, although the significance of this inhibition is unknown.

Applies Your Knowledge
A goiter, or enlargement of the thyroid gland, occurs for many reasons, one of which is a deficiency of iodine in the diet. Explain how iodine deficiency can cause the thyroid gland to enlarge.

Actions of Thyroid Hormones
Thyroid hormones are lipophilic and thus easily cross membranes; the receptors for these hormones are found in the nuclei of target cells. Binding of TH to receptors alters the rate of transcription of mRNA from DNA, thereby altering protein synthesis in the target cell. Such alterations take hours to days to exert an observable effect in the target cell; once induced, however, the effect generally lasts for days.

The primary action of the TH is to raise the body’s BMR—that is, to increase the rate of oxygen consumption and energy expenditure at rest. As a result, heat generation also increases, a phenomenon termed a calorigenic effect. TH-stimulated increases in metabolism occur in most (but not all) tissues of the body; notable exceptions include the brain, spleen, and gonads. One way in which TH increases metabolism is by increasing the rate of Na⁺/K⁺ pump activity in cells. As ATP is hydrolyzed during activity of the Na⁺/K⁺ pump, heat is liberated. Meanwhile, ATP is used up, necessitating higher rates of fuel oxidation and ATP production, which generates even more heat. TH also promotes increased numbers of mitochondria in cells and increases in the concentrations of certain enzymes involved in oxidative phosphorylation.

In addition to stimulating energy utilization, TH promotes increased energy mobilization when present in higher-than-normal concentrations by enhancing glycogenolysis, conversion of muscle proteins to amino acids, and lipolysis. Elevated TH levels also promote gluconeogenesis and ketone synthesis. Conversely, at lower-than-normal concentrations, TH has the opposite effect, promoting glycogenesis and protein synthesis.

Many effects of TH are permissive. This hormone promotes the synthesis of beta adrenergic receptors, for example. Recall that adrenergic receptors bind epinephrine and norepinephrine, the chemical messengers of the sympathetic nervous system. Thus TH permits many tissues to respond to sympathetic neural input and to circulating epinephrine.

Thyroid hormones are necessary for normal growth and development of many other tissues, and for maintaining normal function after growth has ceased. Many of these effects are mediated through stimulation of GH release (in synergism with glucocorticoids, discussed shortly) and permissiveness to GH in target tissues. Developmental actions of TH are especially important with respect to the nervous system. In infants, TH deficiency can lead to a form of irreversible brain damage called cretinism, in which mental development is retarded and growth is stunted. In this condition, axons and dendrites of nerve cells are poorly developed, and myelination of axons is defective. Cretinism can be prevented by early diagnosis of hypothyroidism and initiation of $T_3$ replacement therapy. In the fully developed
nervous system, TH is essential for normal function. In adults, TH deficiency can lead to impairment of mental function, but defects are fully reversible upon restoration of normal TH levels.

21.9 Glucocorticoids
At normal plasma concentrations, the glucocorticoids, which are steroid hormones secreted by the adrenal cortex, maintain a wide variety of essential body functions. At higher concentrations they play a crucial role in the body’s adaptation to stress.

Factors Affecting Secretion of Glucocorticoids
Secretion of glucocorticoids by the adrenal cortex is stimulated by adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn is stimulated by corticotropin releasing hormone (CRH) from the hypothalamus (Figure 21.19). Because glucocorticoids are steroid hormones and, therefore, are lipophilic, glucocorticoids diffuse out of the adrenal cortex and into the bloodstream immediately after synthesis. Plasma glucocorticoid levels are normally regulated by negative feedback on the hypothalamus and anterior pituitary, which limits the secretion of CRH and ACTH, respectively.

Cortisol is the primary glucocorticoid released from the adrenal cortex. Like growth hormone, it is secreted in bursts and exhibits a circadian rhythm. Although the amount of hormone secreted per burst is virtually constant, the burst frequency varies with the time of day: It is higher in the morning and lower at night. This pattern is tied to the sleep-wake cycle and reverses in people who are awake at night and sleep during the day.

Stress, whether physical or emotional, is an important stimulus for cortisol secretion. Those stressors that are most effective in stimulating cortisol secretion are usually noxious stimuli such as surgery, trauma, burns, infection, shock, and pain; other stressors include exposure to temperature extremes, strenuous exercise, and anxiety.

Actions of Glucocorticoids
Although the glucocorticoids do not trigger normal adjustments to the postabsorptive state, their presence is essential to the body’s ability to mobilize fuels in response to signals from other hormones (for example, insulin and glucagon). The primary actions of glucocorticoids are to maintain normal concentrations of enzymes necessary both for the breakdown of proteins, fats, and glycogen, and for the conversion of amino acids to glucose in the liver. For this reason, the glucocorticoids are necessary for survival during prolonged fasting. In their absence, the resulting deficiencies in gluconeogenesis can lead to death by hypoglycemia once glycogen stores have been depleted.

Glucocorticoids are also required for GH secretion (in synergism with TH) and for maintaining the normal responsiveness of blood vessels to vasoconstrictive stimuli such as sympathetic nervous activity, epinephrine, and angiotensin II. In addition, glucocorticoids exert a variety of effects on the functions of the immune system, the nervous system, and the kidneys.

When plasma levels of glucocorticoids increase above resting levels, they exert a number of effects on metabolism that enhance energy mobilization and glucose sparing. In many tissues, they promote decreased uptake of glucose and amino acids. They stimulate lipolysis in adipose tissue, which raises plasma levels of fatty acids and glycerol. At the same time, glucocorticoids stimulate protein breakdown in muscle and other tissues, inhibit protein synthesis, and stimulate gluconeogenesis. As a consequence of all these actions, plasma concentrations of glucose, fatty acids, and amino acids rise.

Glucocorticoids are probably best known for their pharmacological effects when administered at doses that exceed normal physiological levels. At these dosages, glucocorticoids inhibit inflammation and allergic reactions. They are given therapeutically to treat inflammation, such as occurs with arthritis, and to treat certain allergies. Glucocorticoids are also administered during tissue transplantation to decrease the likelihood of rejection, an immune response against foreign tissue. However, glucocorticoids must be administered with caution because these hormones decrease the immune system’s ability to defend the body against pathogens.

The Role of Cortisol in the Stress Response
For decades, cortisol has been considered the hormone of stress. Although it is generally acknowledged that enhanced cortisol secretion is important in helping the body adapt to stress, the reasons for this relationship are poorly understood. Cortisol stimulates energy mobilization, which is useful in tissue repair. The ability to tolerate stress is poor in glucocorticoid-deficient individuals; mortality during recovery from surgery in such persons, for example, is significantly higher than the corresponding rate in normal individuals.

In reality, cortisol is only one facet of the body’s response to stress. In general, if a stimulus is effective in triggering increased cortisol secretion, it also triggers a consistent pattern of other neural and
hormonal responses; for example, stress tends to promote increased activity of the sympathetic nervous system and secretion of epinephrine. These activities elicit the familiar fight-or-flight responses and stimulate gluconeogenesis, glycogenolysis, and lipolysis, which augment cortisol’s energy-mobilizing action. Other changes generally associated with stress include increased secretion of antidiuretic hormone by the posterior pituitary, increased renin release by the kidneys, and elevated plasma levels of angiotensin II. These responses help maintain blood pressure, and thus adequate blood flow to the heart and brain. This generalized, stereotypical pattern of stress responses is referred to as general adaptation syndrome.

**Effects of Abnormal Glucocorticoid Secretion**

An excess or deficiency of glucocorticoid secretion can result from either a defect originating in the adrenal cortex (a primary disorder) or a defect in the secretion of the tropic hormones CRH or ACTH (a secondary disorder).

Hypersecretion of cortisol is associated with a characteristic pattern of signs known as Cushing’s syndrome. These signs include hyperglycemia (due to stimulation of gluconeogenesis and inhibition of glucose uptake) and protein depletion, which results in muscle wasting, weakness, and fragility in many tissues due to the breakdown of connective tissue. A frequent consequence of Cushing’s syndrome is a tendency to bruise easily, which indicates weakened blood vessels. Although cortisol generally has a stimulatory effect on lipolysis, it also stimulates fat synthesis and proliferation of adipocytes in certain regions of the body, which promotes an unusual pattern of body fat distribution: Fat is deposited in the abdomen and above the shoulder blades, giving patients a protruding stomach and a hump-backed appearance; fat is also deposited in the face. Other regions, however, are not affected.

Hyposcetion of cortisol, known as Addison’s disease, is characterized by hypoglycemia and poor tolerance of stress. In the primary form of this disease, which is usually a result of destruction of the adrenal cortex, there is often a defect in the secretion of aldosterone. Because aldosterone normally promotes sodium retention and potassium secretion by the kidneys, Addison’s disease is marked by excess sodium excretion and potassium retention, which by altering plasma sodium and potassium levels results in cardiac arrhythmias and other neuromuscular signs.

**Quick Check 21.5**

1. What does it mean to say that thyroid hormones have a calorigenic effect?
2. Describe the roles of thyrotropin releasing hormone and thyroid stimulating hormone in the regulation of thyroid hormone secretion.
3. Indicate which of the following actions are promoted by glucocorticoids: glycogen synthesis, glycogenolysis, an increase in plasma glucose levels, gluconeogenesis, protein synthesis.
4. How does stress affect glucocorticoid secretion?

The metabolic effects of all the hormones discussed in this chapter are summarized in Table 21.4.

| TABLE 21.4 Summary of the Metabolic Effects of the Hormones Discussed in This Chapter |
|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| **Site of secretion** | **Primary stimuli for secretion (indirect stimuli in parentheses)** | **Net effect on carbohydrate metabolism** | **Effect on plasma glucose** | **Net effect on lipid metabolism** | **Net effect on protein metabolism** |
| Insulin | Beta cells of islets of Langerhans in pancreas | ↑ Plasma glucose | ↑ Glucose uptake into cells | ↑ Plasma glucose | ↑ Triglyceride stores | ↑ Amino acid uptake into cells | ↑ Protein synthesis |
| Glucagon | Alpha cells of islets of Langerhans in pancreas | ↑ Plasma glucose | ↑ Glycogenolysis | ↑ Plasma glucose | ↑ Lipolysis | ↑ Proteolysis |
| Epinephrine | Adrenal medulla | Sympathetic nerve activity (stress, exercise) | ↑ Glycogenolysis | ↑ Plasma glucose | ↑ Lipolysis | None |
| Growth hormone | Anterior pituitary | GHRIH from hypothalamus (↓ plasma glucose, ↓ plasma amino acids, ↓ fatty acids, sleep, stress, exercise) | ↓ Glucose uptake into cells | ↑ Plasma glucose | ↑ Lipolysis | ↑ Amino acid uptake into cells | ↑ Protein synthesis |
| Thyroid hormones (T₃ and T₄) | Thyroid gland | TSH from anterior pituitary (TRH from hypothalamus, cold temperatures in infants) | ↑ Glycogenolysis | None | ↑ Lipolysis | ↑ Protein synthesis |
| Cortisol | Adrenal cortex | ACTH from anterior pituitary (CRH from hypothalamus, stress) | ↓ Glucose uptake into cells | ↑ Plasma glucose | ↑ Lipolysis | ↑ Amino acid uptake into cells | ↑ Proteolysis |
Nowhere is systems integration more apparent than with the endocrine system, and especially the control of whole body metabolism. We learned that the nervous system depends on a constant supply of glucose, but too much glucose causes many complications as evident in diabetes. Glucose enters the blood through absorption from the gastrointestinal tract during the absorptive state and mostly from synthesis by the liver (gluconeogenesis and glycogenolysis) during the postabsorptive state. The pancreatic hormones insulin and glucagon regulate whole body metabolism, but so do cortisol, epinephrine, growth hormone, and insulin-like growth factor during periods of stress and growth. The sympathetic nervous system contributes to regulation of blood glucose during stress and the postabsorptive state and the parasympathetic nervous system promotes absorption of nutrients during the absorptive state.

For the endocrine system to regulate metabolism, growth, and coping with stress requires that the cardiovascular system does its job of delivering blood (containing these hormones) to the target tissues. The respiratory system functions in providing oxygen needed to generate most of the body’s ATP and removing carbon dioxide produced during this process. Skeletal muscle’s high metabolic rate helps maintain energy balance by utilizing nutrients, and smooth muscle functions indirectly through its role in other systems such as the cardiovascular, respiratory, and gastrointestinal systems.

The endocrine system affects every organ system, by altering its metabolism as described in this chapter or by altering function of the various organ systems as described throughout the book. For example, antidiuretic hormone regulates water reabsorption by the kidneys and total peripheral resistance, both of which are important in controlling blood pressure. The gastrointestinal hormone CCK regulates not only gastrointestinal function but also food intake. As we learned in this chapter, glucocorticoids suppress the immune system and growth, both detrimental effects observed when a person is subjected to chronic stress.

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#### How Are Insulin Pathways Involved in Diabetes Pathogenesis and Treatment?

Tenzin, a 35-year-old female, is 5 feet, 8 inches and weighs 250 pounds. She works, goes to school, has a 6-month-old baby, and has very little time to cook meals at home or to exercise.

Tenzin’s mother had gestational diabetes when she was pregnant with Tenzin, and Tenzin also had gestational diabetes during her recent pregnancy. Because of this, Tenzin is being monitored for the development of diabetes.

Tenzin’s initial postpartum test results are below.

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Test</strong></td>
</tr>
<tr>
<td>Glucose (fasting)</td>
</tr>
<tr>
<td>Oral glucose tolerance test</td>
</tr>
</tbody>
</table>

According to her test results, Tenzin has ____.

A. prediabetes
B. normal values
C. diabetes mellitus
D. diabetes insipidus

*Additional questions from this Solve It activity can be assigned in MasteringA&P.

### CHAPTER REVIEW

#### SUMMARY

21.1 An Overview of Whole-Body Metabolism, p. 603
- Whole-body metabolism requires the coordination of cellular metabolic activities.
- Cells use energy in the form of ATP, which they obtain from the oxidation of small nutrient molecules such as glucose, fatty acids, and amino acids.

21.2 Energy Intake, Utilization, and Storage, p. 604
- Energy is released in cells by the breakdown of nutrients into smaller molecules, as when glucose, amino acids, or fatty acids are oxidized to yield waste products.
- Energy mobilization comprises the breakdown of macromolecules into small nutrient molecules that are released into the bloodstream.
- Energy is stored by converting small nutrient molecules into macromolecules.
Glucose is stored as glycogen in skeletal muscle and liver. Fatty acids and glycerol are stored as triglycerides in adipose tissue. Amino acids are stored as proteins in all cells, but especially in skeletal muscle cells.

**21.3 Energy Balance, p. 605**
- Energy input must equal energy output to maintain energy balance.
- Energy input comes from ingested nutrients, whereas energy output is the energy expended as heat or work.
- Positive energy balance occurs when energy input exceeds energy output; negative energy balance occurs when energy output exceeds energy input.
- The body’s metabolic rate is the total amount of energy released per unit time as a result of nutrient oxidation.
- The metabolic rate at rest is the basal metabolic rate (BMR).

**21.4 Energy Metabolism During the Absorptive and Postabsorptive States, p. 607**
- When the body is in an absorptive state, glucose is used by most tissues as the primary fuel.
- Absorbed nutrients are also converted to glycogen, triglycerides, and proteins.
- Excess amino acids and glucose are mostly converted to fatty acids and stored as triglycerides.
- When the body is in a postabsorptive state, stored glycogen, triglycerides, and proteins are catabolized for energy.
- Fatty acids are used by most tissues as the primary fuel.
- The nervous system, unlike most other tissues, relies on a steady supply of glucose for its energy.
- Utilization of nonglucose fuels conserves glucose for use by the nervous system, a phenomenon called glucose sparing.
- The liver is able to produce more glucose by gluconeogenesis.

**21.5 Regulation of Absorptive and Postabsorptive Metabolism, p. 611**
- Metabolic adjustments to the absorptive state are promoted by insulin; they include synthesis of energy stores and uptake of glucose and amino acids by cells in many tissues.
- Insulin also suppresses gluconeogenesis and regulates plasma glucose levels via negative feedback control.
- Metabolic adjustments to the postabsorptive state promoted by glucagon include glycogenolysis, protein breakdown by the liver, lipolysis, gluconeogenesis, and ketone synthesis.
- Glucagon also helps to regulate blood glucose levels.
- Other postabsorptive metabolic adjustments are promoted by increased epinephrine secretion and sympathetic nervous activity.

**21.6 Thermoregulation, p. 616**
- The thermoregulatory system acts to maintain a constant core temperature through thermoregulatory centers in the hypothalamus; central and peripheral thermoreceptors that detect core and skin temperature, respectively; and effector organs including cutaneous blood vessels, sweat glands, and skeletal muscle.
- Changes in cutaneous blood flow regulate body temperature when environmental temperature is within the thermoneutral zone.
- When the environmental temperature is lower than the thermoneutral zone, shivering is also needed to generate heat.
- When the environmental temperature is higher than the thermoneutral zone, sweating contributes to heat loss through evaporation.

**21.7 Hormonal Regulation of Growth, p. 619**
- Body growth during childhood is promoted by the actions of growth hormone (GH), which is secreted by the anterior pituitary and acts to promote the growth of soft tissues and bones.
- In adulthood, GH acts to maintain bone mass and lean body mass.
- Actions promoted by GH include hyper trophy, hyperplasia, protein synthesis, lipolysis, gluconeogenesis, and amino acid uptake by cells.
- GH also inhibits glucose uptake by adipose tissue and muscle.
- Combined metabolic actions work to raise plasma levels of glucose, fatty acids and glycerol, thereby making energy more readily available to growing tissues.
- Many GH actions are mediated by IGFs synthesized by the liver and other tissues.

**21.8 Thyroid Hormones, p. 624**
- Thyroid hormone (TH) is normally secreted by the thyroid gland at near-constant rates and increases the metabolic rate in most tissues of the body.
- At high concentrations, TH mobilizes energy stores.
- TH is necessary for normal growth, development, and maintenance of normal function in many tissues, particularly the nervous system.
- TH is secreted in two forms: $I_3$, the more active form, and $I_4$, the more abundant form.

**21.9 Glucocorticoids, p. 626**
- Glucocorticoids are released by the adrenal cortex and are important in the body’s response to stress.
- Glucocorticoids are also required so that the body can mobilize energy stores during postabsorptive periods.

**EXERCISES**

**Multiple-Choice Questions**

1. Which of the following is an example of a permissive effect of a hormone?
   a) The effect of thyroid hormones on growth
   b) The effect of insulin on glucose uptake by cells
   c) The effect of sex hormones on the secretion of growth hormone
   d) Both a and c
   e) All of the above

2. Which of the following is an example of a glucose-sparing effect of cortisol?
   a) Inhibition of ACTH release
   b) Stimulation of gluconeogenesis by the liver
   c) Stimulation of lipolysis
   d) Stimulation of glycogen breakdown
   e) Stimulation of protein synthesis

3. Which of the following cells of the pancreas secrete insulin?
   a) Alpha cells
   b) Beta cells
   c) Delta cells
   d) Exocrine cells
   e) Duct cells
4. Stress stimulates secretion of which of the following hormones?
   a) Growth hormone
   b) Epinephrine
   c) Thyroid hormones
   d) ACTH
   e) All of the above

5. Hypoglycemia inhibits secretion of which of the following?
   a) Growth hormone
   b) Insulin
   c) Epinephrine
   d) Glucagon
   e) All of the above

6. In the postabsorptive state, the central nervous system uses which of the following as its primary source of energy?
   a) Fatty acids
   b) Amino acids
   c) Glucose
   d) Glycerol
   e) Ketones

7. Which of the following cell types is directly responsible for building new bone material?
   a) Osteoblasts
   b) Osteoclasts
   c) Osteocytes
   d) Chondrocytes

8. Which of the following is true of adulthood?
   a) Growth hormone exerts no effects on body tissues.
   b) The secretion of growth hormone ceases altogether.
   c) Growth hormone cannot stimulate increases in the length of long bones.
   d) The structure of bone becomes permanently fixed.
   e) None of the above

9. Which form of thyroid hormone has greater activity at target cells?
   a) T3
   b) T4
   c) Neither; T3 and T4 have equal activity

10. Which of the following hormones is a steroid?
    a) Thyroid hormones
    b) Insulin
    c) Glucagon
    d) Growth hormone
    e) Cortisol

**Objective Questions**

11. Energy mobilization is promoted by (insulin/glucagon).

12. Secretion of (insulin/glucagon) is increased during the absorptive period.

13. Insulin and glucagon both help regulate the plasma glucose concentration. (true/false)

14. Breakdown of triglycerides yields fatty acids and ____, which can be used by cells for energy.

15. Conversion of amino acids to fatty acids is more likely to occur in the (absorptive/postabsorptive) state.

16. Conversion of amino acids to glucose is more likely to occur in the (absorptive/postabsorptive) state.

17. An increase in plasma thyroid hormone levels tends to make the body’s energy balance more (positive/negative).

18. Energy that is taken into the body is either stored or appears as work or ____.

19. Stress tends to (stimulate/inhibit) GHRH secretion.

20. Many of growth hormone’s effects on target tissues are due to it triggering release of other chemical messengers called ____.

21. Closure of the epiphyseal plates is promoted by (growth hormone/sex hormones).

22. Thyroid hormones promote increased responsiveness of target tissues to (sympathetic/parasympathetic) nerve activity.

23. Glucocorticoids promote (increased/decreased) plasma glucose levels.

24. Stimulation of gluconeogenesis by glucagon is an example of a glucose-sparing effect. (true/false)

25. Plasma glucocorticoids have a(n) (stimulatory/inhibitory) effect on the secretion of ACTH.

**Essay Questions**

26. Describe the regulation of plasma glucose by insulin and glucagon. Include a description of the role of negative feedback.

27. Describe how insulin, glucagon, and the sympathetic nervous system work together to maintain adequate plasma glucose levels during fasting. Why is this coordination important?

28. Describe the various factors that determine the body’s energy balance. Be sure to describe what happens to energy that is liberated as a result of fuel oxidation.

29. Describe the similarities between the metabolic actions of thyroid hormones and glucocorticoids.

30. Describe the metabolic actions of growth hormone, and explain how these actions promote growth.

**Critical Thinking**

31. Some athletes have used anabolic steroids in hopes of enhancing their athletic performance. Which type of steroids might they use? Based on what you read in this chapter, what could be some of the deleterious effects of taking such steroids?

32. Many hormone deficiencies are genetic in origin. Explain how a steroid hormone deficiency can be caused by a mutant gene.

33. Physicians often recommend that people with hypoglycemia consume several small meals per day, as opposed to the typical three large meals per day. Explain how this dietary pattern can affect insulin and glucagon levels in the blood, and ultimately blood glucose levels.

34. An obese patient goes to his doctor complaining of lethargy. The doctor suspects that the patient has hypothyroidism, but does not know whether the disorder would be primary or secondary. Which tests should the doctor run to determine whether hypothyroidism exists, and if it does, whether it is primary or secondary? Explain the expected results if the patient has a tumor in the hypothalamus that is affecting the release of TRH.

Answers to the Figure Questions, Apply Your Knowledge, Multiple-Choice Questions, and Objective Questions are located at the back of the book. Answer to Solve It activity: A