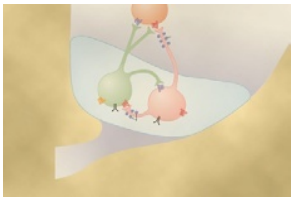
CHAPTER 71

Dietary Balances; Regulation of Feeding; Obesity and Starvation; Vitamins and Minerals



Energy Intake and Output Are Balanced Under Steady-State Conditions

Intake of carbohydrates, fats, and proteins provides energy that can be used to perform various body functions or stored for later use. Stability of body weight and composition over long periods requires that a person's energy intake and energy expenditure be balanced. When a person is overfed and energy intake persistently exceeds expenditure, most of the excess energy is stored as fat, and body weight increases; conversely, loss of body mass and starvation occur when energy intake is insufficient to meet the body's metabolic needs.

Because different foods contain different proportions of proteins, carbohydrates, fats, minerals, and vitamins, appropriate balances must also be maintained among these constituents so that all segments of the body's metabolic systems can be supplied with the requisite materials. This chapter discusses the mechanisms by which food intake is regulated in accordance with the body's metabolic needs and some of the problems of maintaining balance among the different types of foods.

Dietary Balances

Energy Available in Foods

The energy liberated from each gram of carbohydrate as it is oxidized to carbon dioxide and water is 4.1 Calories (1 Calorie equals 1 kilocalorie), and that liberated from fat is 9.3 Calories. The energy liberated from metabolism of the average dietary protein as each gram is oxidized to carbon dioxide, water, and urea is 4.35 Calories. Also, these substances vary in the average percentages that are absorbed from the gastrointestinal tract: about 98 percent of carbohydrate, 95 percent of fat, and 92 percent of protein. Therefore, the average *physiologically available energy* in each gram of these three foodstuffs is as follows:

	Calories
Carbohydrate	4
Fat	9
Protein	4

Average Americans receive about 15 percent of their energy from protein, 40 percent from fat, and 45 percent from carbohydrate. In most non-Western countries, the quantity of energy derived from carbohydrates far exceeds that derived from both proteins and fats. Indeed, in some parts of the world where meat is scarce, the energy received from fats and proteins combined may be no greater than 15 to 20 percent.

Table 71-1 gives the compositions of selected foods, demonstrating especially the high proportions of fat and protein in meat products and the high proportion of carbohydrate in most vegetable and grain products. Fat is deceptive in the diet because it usually exists as nearly 100 percent fat, whereas both proteins and carbohydrates are mixed in watery media so that each of these normally represents less than 25 percent of the weight. Therefore, the fat of one pat of butter mixed with an entire helping of potato sometimes contains as much energy as the potato itself.

Average Daily Requirement for Protein Is 30 to 50 Grams. Twenty to 30 grams of the body proteins are degraded and used to produce other body chemicals daily. Therefore, all cells must continue to form new proteins to take the place of those that are being destroyed, and a supply of protein is necessary in the diet for this purpose. An average person can maintain normal stores of protein, provided the *daily intake is above 30 to 50 grams*.

Some proteins have inadequate quantities of certain essential amino acids and therefore cannot be used to replace the degraded proteins. Such proteins are called *partial proteins*, and when they are present in large quantities in the diet, the daily protein requirement is much greater than normal. In general, proteins derived from animal foodstuffs are more complete than are proteins derived from vegetable and grain sources. For example, the protein of corn has almost no tryptophan, one of the essential amino acids. Therefore, individuals in low-income countries who consume cornmeal as the principal source of protein sometimes develop the protein-deficiency syndrome called *kwashiorkor*, which consists of failure to grow, lethargy, depressed mentality, and edema caused by low plasma protein concentration.

Carbohydrates and Fats Act as "Protein Sparers." When the diet contains an abundance of carbohydrates and fats, almost all the body's energy is derived from these two substances, and little is derived from proteins.

Therefore, both carbohydrates and fats are said to be *protein sparers*. Conversely, in starvation, after the carbohydrates and fats have been depleted, the body's protein

Table 71-1 Protein, Fat, and Carbohydrate Content of Different Foods

Food	% Protein	% Fat	% Carbohydrate	Fuel Value per 100 Grams (Calories)
Apples	0.3	0.4	14.9	64
Asparagus	2.2	0.2	3.9	26
Bacon, fat	6.2	76.0	0.7	712
broiled	25.0	55.0	1.0	599
Beef (average)	17.5	22.0	1.0	268
Beets, fresh	1.6	0.1	9.6	46
Bread, white	9.0	3.6	49.8	268
Butter	0.6	81.0	0.4	733
Cabbage	1.4	0.2	5.3	29
Carrots	1.2	0.3	9.3	45
Cashew nuts	19.6	47.2	26.4	609
Cheese, cheddar, American	23.9	32.3	1.7	393
Chicken, total edible	21.6	2.7	1.0	111
Chocolate	5.5	52.9	18.0	570
Corn (maize)	10.0	4.3	73.4	372
Haddock	17.2	0.3	0.5	72
Lamb, leg (average)	18.0	17.5	1.0	230
Milk, fresh whole	3.5	3.9	4.9	69
Molasses	0.0	0.0	60.0	240
Oatmeal, dry, uncooked	14.2	7.4	68.2	396
Oranges	0.9	0.2	11.2	50
Peanuts	26.9	44.2	23.6	600
Peas, fresh	6.7	0.4	17.7	101
Pork, ham	15.2	31.0	1.0	340
Potatoes	2.0	0.1	19.1	85
Spinach	2.3	0.3	3.2	25
Strawberries	0.8	0.6	8.1	41
Tomatoes	1.0	0.3	4.0	23
Tuna, canned	24.2	10.8	0.5	194
Walnuts, English	15.0	64.4	15.6	702

stores are consumed rapidly for energy, sometimes at rates approaching several hundred grams per day rather than the normal daily rate of 30 to 50 grams.

Methods for Determining Metabolic Utilization of Carbohydrates, Fats, and Proteins

"Respiratory Quotient" Is the Ratio of CO_2 Production to O_2 Utilization and Can Be Used to Estimate Fat and Carbohydrate Utilization. When carbohydrates are metabolized with oxygen, exactly one carbon dioxide molecule is formed for each molecule of oxygen consumed. This ratio of carbon dioxide output to oxygen usage is called the *respiratory quotient*, so the respiratory quotient for carbohydrates is 1.0.

When fat is oxidized in the body's cells, an average of 70 carbon dioxide molecules are formed for each 100 molecules of oxygen consumed. The respiratory quotient for the metabolism of fat therefore averages 0.70. When proteins are oxidized by the cells, the average respiratory quotient is 0.80. The reason that the respiratory quotients for fats and proteins are lower than those for carbohydrates is that a portion of the oxygen metabolized with these foods is required to combine with the excess hydrogen atoms present in their molecules, so less carbon dioxide is formed in relation to the oxygen used.

Now let us see how one can make use of the respiratory quotient to determine the relative utilization of different foods by the body. First, it will be recalled from Chapter 39 that the output of carbon dioxide by the lungs divided by the uptake of oxygen during the same period is called the *respiratory exchange ratio*. Over a period of 1 hour or more, the respiratory exchange ratio exactly equals the average respiratory quotient of the metabolic reactions throughout the

body. If a person has a respiratory quotient of 1.0, he or she is metabolizing almost entirely carbohydrates, because the respiratory quotients for both fat and protein metabolism are considerably less than 1.0. Likewise, when the respiratory quotient is about 0.70, the body is metabolizing almost entirely fats, to the exclusion of carbohydrates and proteins. And, finally, if we ignore the normally small amount of protein metabolism, respiratory quotients between 0.70 and 1.0 describe the approximate ratios of carbohydrate to fat metabolism. To be more exact, one can first determine the protein utilization by measuring nitrogen excretion as discussed in the next section. Then, using the appropriate mathematical formula, one can calculate almost exactly the utilization of the three foodstuffs.

Some of the important findings from studies of respiratory quotients are the following:

1. Immediately after a meal, almost all the food that is metabolized is carbohydrates, so the respiratory quotient at that time approaches 1.0.
2. About 8 to 10 hours after a meal, the body has already used up most of its readily available carbohydrates, and the respiratory quotient approaches that for fat metabolism, about 0.70.
3. In untreated diabetes mellitus, little carbohydrate can be used by the body's cells under any conditions because insulin is required for this. Therefore, when diabetes is severe, most of the time the respiratory quotient remains near that for fat metabolism, 0.70.

Nitrogen Excretion Can Be Used to Assess Protein Metabolism. The average protein contains about 16 percent nitrogen. During metabolism of the protein, about 90 percent of this nitrogen is excreted in the urine in the form of urea, uric acid, creatinine, and other nitrogen products. The remaining 10 percent is excreted in the feces. Therefore, the rate of protein breakdown in the body can be estimated by measuring the amount of nitrogen in the urine, then adding 10 percent for the nitrogen excreted in the feces, and multiplying by 6.25 (i.e., 100/16) to determine the total amount of protein metabolism in grams per day. Thus, excretion of 8 grams of nitrogen in the urine each day means that there has been about 55 grams of protein breakdown. If the daily intake of protein is less than the daily breakdown of protein, the person is said to have a *negative nitrogen balance*, which means that his or her body stores of protein are decreasing daily.

Regulation of Food Intake and Energy Storage

Stability of the body's total mass and composition over long periods requires that energy intake match energy expenditure. As discussed in Chapter 72, only about 27 percent of the energy ingested normally reaches the functional systems of the cells, and much of this is eventually converted to heat, which is generated as a result of protein metabolism, muscle activity, and activities of the various organs and tissues of the body. Excess energy intake is stored mainly as fat, whereas a deficit of energy intake causes loss of total body mass until energy expenditure eventually equals energy intake or death occurs.

Although there is considerable variability in the amount of energy storage (i.e., fat mass) in different individuals, maintenance of an adequate energy supply is necessary for survival. Therefore, the body is endowed with powerful physiologic control systems that help maintain adequate energy intake. Deficits of energy stores, for example, rapidly activate multiple mechanisms that cause hunger and drive a person to seek food. In athletes and laborers, energy expenditure for the high level of muscle activity may be as high as 6000 to 7000 Calories per day, compared with only about 2000 Calories per day for sedentary individuals. Thus, a large energy expenditure associated with physical work usually stimulates equally large increases in caloric intake.

What are the physiological mechanisms that sense changes in energy balance and influence the quest for food? Maintenance of adequate energy supply in the body is so critical that there are multiple short-term and long-term control systems that regulate not only food intake but also energy expenditure and energy stores. In the next few sections we describe some of these control systems and their operation in physiological conditions, as well as in obesity and starvation.

Neural Centers Regulate Food Intake

The sensation of *hunger* is associated with a craving for food and several other physiological effects, such as rhythmical contractions of the stomach and restlessness, which cause the person to seek an adequate food supply. A person's *appetite is a desire for food*, often of a particular type, and is useful in helping to choose the quality of the food to be eaten. If the quest for food is successful, the feeling of *satiety* occurs. Each of these feelings is influenced by environmental and cultural factors, as well as by physiologic controls that influence specific centers of the brain, especially the hypothalamus.

The Hypothalamus Contains Hunger and Satiety Centers. Several neuronal centers of the hypothalamus participate in the control of food intake. The *lateral nuclei of the hypothalamus serve as a feeding center*, and stimulation of this area causes an animal to eat voraciously *(hyperphagia)*. Conversely, destruction of the lateral hypothalamus causes lack of desire for food and progressive *inanition*, a condition characterized by marked weight loss, muscle weakness, and decreased metabolism. The lateral hypothalamic feeding center operates by exciting the motor drives to search for food.

The *ventromedial nuclei of the hypothalamus serve as the satiety center*. This center is believed to give a sense of nutritional satisfaction that inhibits the feeding center. Electrical stimulation of this region can cause complete satiety, and even in the presence of highly appetizing food, the animal refuses to eat *(aphagia)*. Conversely, destruction of the ventromedial nuclei causes voracious and continued eating until the animal becomes extremely obese, sometimes weighing as much as four times normal.

The *paraventricular, dorsomedial*, and *arcuate nuclei* of the hypothalamus also play a major role in regulating food intake. For example, lesions of the paraventricular nuclei often cause excessive eating, whereas lesions of the dorsomedial nuclei usually depress eating behavior. As discussed later, the arcuate nuclei are the sites in the hypothalamus where multiple hormones released from the gastrointestinal tract and adipose tissue converge to regulate food intake, as well as energy expenditure.

There is much chemical cross-talk among the neurons on the hypothalamus, and together, these centers coordinate the processes that control eating behavior and the perception of satiety. These hypothalamic nuclei also influence the secretion of several hormones that are important in regulating energy balance and metabolism, including those from the thyroid and adrenal glands, as well as the pancreatic islet cells.

The hypothalamus receives neural signals from the gastrointestinal tract that provide sensory information about stomach filling; chemical signals from nutrients in the blood (glucose, amino acids, and fatty acids) that signify satiety; signals from gastrointestinal hormones; signals from hormones released by adipose tissue; and signals from the cerebral cortex (sight, smell, and taste) that influence feeding behavior. Some of these inputs to the hypothalamus are shown in Figure 71-1.

The hypothalamic feeding and satiety centers have a high density of receptors for neurotransmitters and hormones that influence feeding behavior. A few of the many substances that have been shown to alter appetite and feeding behavior in experimental studies are listed in Table 71-2 and are generally categorized as (1) *orexigenic* substances that stimulate feeding or (2) *anorexigenic* substances that inhibit feeding.

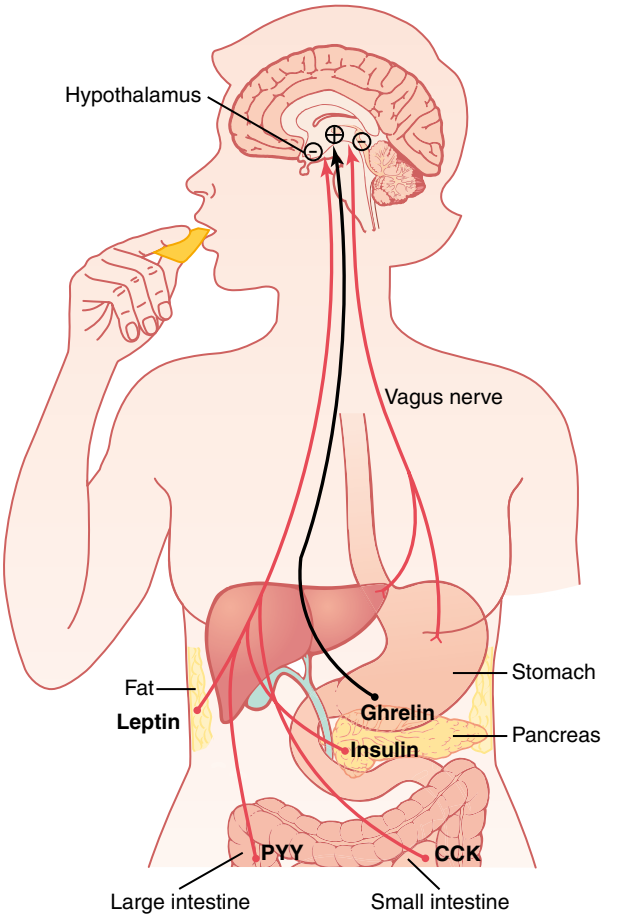


Figure 71-1 Feedback mechanisms for control of food intake. Stretch receptors in the stomach activate sensory afferent pathways in the vagus nerve and inhibit food intake. Peptide YY (*PYY*), cholecystokinin (*CCK*), and insulin are gastrointestinal hormones that are released by the ingestion of food and suppress further feeding. Ghrelin is released by the stomach, especially during fasting, and stimulates appetite. Leptin is a hormone produced in increasing amounts by fat cells as they increase in size; it inhibits food intake.

Neurons and Neurotransmitters in the Hypothalamus That Stimulate or Inhibit Feeding. There are two distinct types of neurons in the arcuate nuclei of the hypothalamus that are especially important as controllers of both appetite and energy expenditure (Figure 71-2): (1) *pro-opiomelanocortin (POMC) neurons* that produce α-melanocyte-stimulating hormone (α-MSH) together with cocaine- and amphetamine-related transcript (CART) and (2) *neurons that produce the orexigenic substances neuropeptide Y (NPY) and agouti-related protein (AGRP)*. Activation of the POMC neurons decreases food intake and increases energy expenditure, whereas activation of the NPY-AGRP neurons increases food intake and reduces energy expenditure. As discussed later, these neurons appear to be the major targets for several hormones that regulate appetite, including *leptin*, *insulin*, *cholecystokinin (CCK)*, and *ghrelin*. In fact, the neurons of the arcuate nuclei appear to be a site of convergence of many of the nervous and peripheral signals that regulate energy stores.

The POMC neurons release α-MSH, which then acts on *melanocortin receptors* found especially in neurons of the *paraventricular nuclei*. Although there are at least five subtypes of melanocortin receptors (MCR), *MCR-3* and *MCR-4* are especially important in regulating food intake and energy balance. Activation of these receptors reduces food intake while increasing energy expenditure. Conversely, inhibition of MCR-3 and MCR-4 greatly increases food intake and decreases energy expenditure. The effect of MCR activation to increase energy expenditure appears to be mediated, at least in part, by activation of neuronal pathways that project from the paraventricular nuclei to the *nucleus tractus solitarius* and stimulate sympathetic nervous system activity.

The hypothalamic melanocortin system plays a powerful role in regulating energy stores of the body, and defective signaling of the melanocortin pathway is associated with extreme obesity. In fact, mutations of MCR-4 represent the most common known monogenic (single-gene) cause of human obesity, and some studies suggest that MCR-4 mutations may account for as much as 5 to 6 percent of early-onset severe obesity in children. In contrast, excessive activation of the melanocortin system reduces appetite. Some studies suggest that this activation may

Table 71-2 Neurotransmitters and Hormones That Influence Feeding and Satiety Centers in the Hypothalamus

Decrease Feeding (Anorexigenic)	Increase Feeding (Orexigenic)
α-Melanocyte-stimulating hormone (α-MSH)	Neuropeptide Y (NPY)
Leptin	Agouti-related protein (AGRP)
Serotonin	Melanin-concentrating hormone (MCH)
Norepinephrine	Orexins A and B
Corticotropin-releasing hormone	Endorphins
Insulin	Galanin (GAL)
Cholecystokinin (CCK)	Amino acids (glutamate and γ-aminobutyric acid)
Glucagon-like peptide (GLP)	Cortisol
Cocaine- and amphetamine-regulated transcript (CART)	Ghrelin
Peptide YY (PYY)	Endocannabinoids

play a role in causing the anorexia associated with severe infections, cancer tumors, or uremia.

AGRP released from the orexigenic neurons of the hypothalamus is a natural antagonist of MCR-3 and MCR-4 and probably increases feeding by inhibiting the effects of α-MSH to stimulate melanocortin receptors (see Figure 71-2). Although the role of AGRP in normal physiologic control of food intake is unclear, excessive formation of AGRP in mice and humans, due to gene mutations, is associated with increased food intake and obesity.

NPY is also released from orexigenic neurons of the arcuate nuclei. When energy stores of the body are low, orexigenic neurons are activated to release NPY, which stimulates appetite. At the same time, firing of the POMC neurons is reduced, thereby decreasing the activity of the melanocortin pathway and further stimulating appetite.

Neural Centers That Influence the Mechanical Process of Feeding. Another aspect of feeding is the mechanical act of the feeding process itself. If the brain is sectioned below the hypothalamus but above the mesencephalon, the animal can still perform the basic mechanical features of the feeding process. It can salivate, lick its lips,

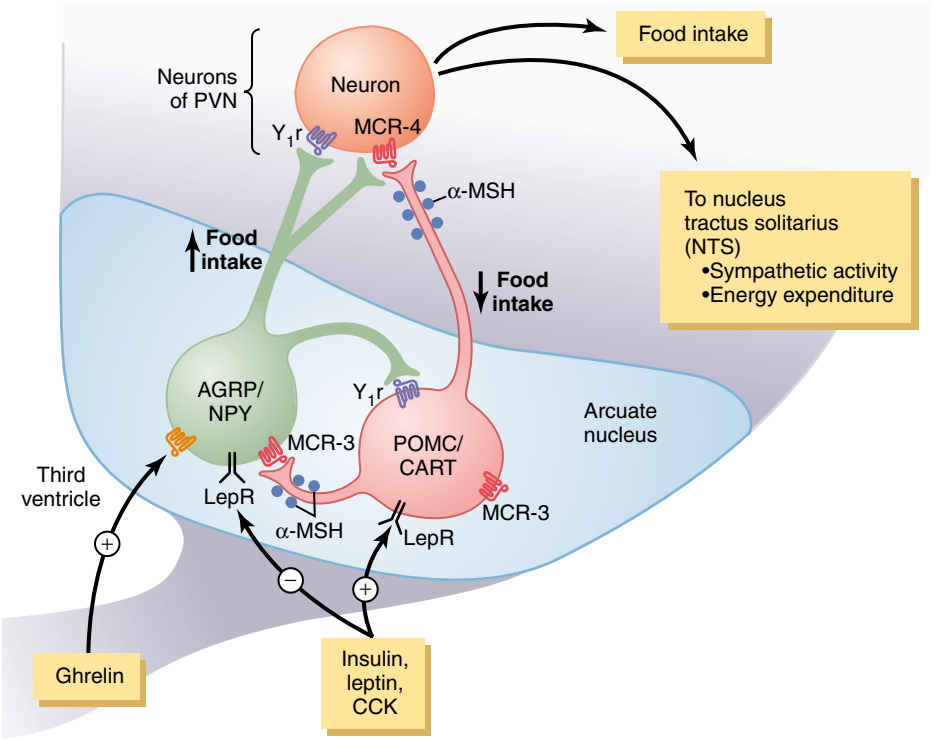


Figure 71-2 Control of energy balance by two types of neurons of the arcuate nuclei: (1) pro-opiomelanocortin (*POMC*) neurons that release α-melanocyte-stimulating hormone (*α-MSH*) and cocaine- and amphetamine-regulated transcript (*CART*), decreasing food intake and increasing energy expenditure and (2) neurons that produce agouti-related protein (*AGRP*) and neuropeptide Y (*NPY*), increasing food intake and reducing energy expenditure. α-MSH released by POMC neurons stimulates melanocortin receptors (*MCR-3* and *MCR-4*) in the paraventricular nuclei (*PVN*), which then activate neuronal pathways that project to the nucleus tractus solitarius (*NTS*) and increase sympathetic activity and energy expenditure. AGRP acts as an antagonist of MCR-4. Insulin, leptin, and cholecystokinin (*CCK*) are hormones that inhibit AGRP-NPY neurons and stimulate adjacent POMC-CART neurons, thereby reducing food intake. Ghrelin, a hormone secreted from the stomach, activates AGRP-NPY neurons and stimulates food intake. LepR, leptin receptor; Y_1R, neuropeptide Y1 receptor. (Redrawn from Barsh GS, Schwartz MW: Nature Rev Genetics 3:589, 2002.)

chew food, and swallow. Therefore, *the actual mechanics of feeding are controlled by centers in the brain stem*. The function of the other centers in feeding, then, is to control the quantity of food intake and to excite these centers of feeding mechanics to activity.

Neural centers higher than the hypothalamus also play important roles in the control of feeding, particularly in the control of appetite. These centers include the *amygdala* and the *prefrontal cortex*, which are closely coupled with the hypothalamus. It will be recalled from the discussion of the sense of smell in Chapter 53 that portions of the amygdala are a major part of the olfactory nervous system. Destructive lesions in the amygdala have demonstrated that some of its areas increase feeding, whereas others inhibit feeding. In addition, stimulation of some areas of the amygdala elicits the mechanical act of feeding. An important effect of destruction of the amygdala on both sides of the brain is a "psychic blindness" in the choice of foods. In other words, the animal (and presumably the human being as well) loses or at least partially loses the appetite control that determines the type and quality of food it eats.

Factors That Regulate Quantity of Food Intake

Regulation of the quantity of food intake can be divided into *short-term regulation*, which is concerned primarily with preventing overeating at each meal, and *long-term regulation*, which is concerned primarily with maintenance of normal quantities of energy stores in the body.

Short-Term Regulation of Food Intake

When a person is driven by hunger to eat voraciously and rapidly, what turns off the eating when he or she has eaten enough? There has not been enough time for changes in the body's energy stores to occur, and it takes hours for enough nutritional factors to be absorbed into the blood to cause the necessary inhibition of eating. Yet it is important that the person not overeat and that he or she eat an amount of food that approximates nutritional needs. The following are several types of rapid feedback signals that are important for these purposes.

Gastrointestinal Filling Inhibits Feeding. When the gastrointestinal tract becomes distended, especially the stomach and the duodenum, stretch inhibitory signals are transmitted mainly by way of the vagi to suppress the feeding center, thereby reducing the desire for food (see Figure 71-1).

Gastrointestinal Hormonal Factors Suppress Feeding. *Cholecystokinin (CCK)*, released mainly in response to fat and proteins entering the duodenum, enters the blood and acts as a hormone to influence several gastrointestinal functions such as gallbladder contraction, gastric emptying, gut motility, and gastric acid secretion as discussed in Chapters 62, 63, and 64. However, CCK also activates receptors on local sensory nerves in the duodenum, sending messages to the brain via the vagus nerve that contribute to satiation and meal cessation. The effect of CCK is short-lived and chronic administration of CCK by itself has no major effect on body weight. Therefore, CCK functions mainly to prevent overeating during meals but may not play a major role in the frequency of meals or the total energy consumed.

Peptide YY (PYY) is secreted from the entire gastrointestinal tract, but especially from the ileum and colon. Food intake stimulates release of PYY, with blood concentrations rising to peak levels 1 to 2 hours after ingesting a meal. These peak levels of PYY are influenced by the number of calories ingested and the composition of the food, with higher levels of PYY observed after meals with a high fat content. Although injections of PYY into mice have been shown to decrease food intake for 12 hours or more, the importance of this gastrointestinal hormone in regulating appetite in humans is still unclear.

For reasons that are not entirely understood, the presence of food in the intestines stimulates them to secrete *glucagon-like peptide (GLP)*, which in turn enhances glucose-dependent *insulin* production and secretion from the pancreas. Glucagon-like peptide and insulin both tend to suppress appetite. Thus, eating a meal stimulates the release of several gastrointestinal hormones that may induce satiety and reduce further intake of food (see Figure 71-1).

Ghrelin—a Gastrointestinal Hormone—Increases Feeding. *Ghrelin* is a hormone released mainly by the oxyntic cells of the stomach but also, to a much less extent, by the intestine. Blood levels of ghrelin rise during fasting, peak just before eating, and then fall rapidly after a meal, suggesting a possible role in stimulating feeding. Also, administration of ghrelin increases food intake in experimental animals, further supporting the possibility that it may be an orexigenic hormone. However, its physiologic role in humans is still uncertain.

Oral Receptors Meter Food Intake. When an animal with an esophageal fistula is fed large quantities of food, even though this food is immediately lost again to the exterior, the degree of hunger is decreased after a reasonable quantity of food has passed through the mouth. This effect occurs despite the fact that the gastrointestinal tract does not become the least bit filled. Therefore, it is postulated that various "oral factors" related to feeding, such as chewing, salivation, swallowing, and tasting, "meter" the food as it passes through the mouth, and after a certain amount has passed, the hypothalamic feeding center becomes inhibited. However, the inhibition caused by this metering mechanism is considerably less intense and of shorter duration, usually lasting for only 20 to 40 minutes, than is the inhibition caused by gastrointestinal filling.

Intermediate and Long-Term Regulation of Food Intake

An animal that has been starved for a long time and is then presented with unlimited food eats a far greater quantity than does an animal that has been on a regular diet. Conversely, an animal that has been force-fed for several

weeks eats very little when allowed to eat according to its own desires. Thus, the feeding control mechanism of the body is geared to the nutritional status of the body.

Effect of Blood Concentrations of Glucose, Amino Acids, and Lipids on Hunger and Feeding. It has long been known that a decrease in blood glucose concentration causes hunger, which has led to the so-called *glucostatic theory of hunger and feeding regulation*. Similar studies have demonstrated the same effect for blood amino acid concentration and blood concentration of breakdown products of lipids such as the keto acids and some fatty acids, leading to the *aminostatic* and *lipostatic* theories of regulation. That is, when the availability of any of the three major types of food decreases, the desire for feeding is increased, eventually returning the blood metabolite concentrations back toward normal.

Neurophysiological studies of function in specific areas of the brain also support the glucostatic, aminostatic, and lipostatic theories, by the following observations: (1) A rise in blood *glucose* level *increases the rate of firing of glucoreceptor neurons in the satiety center in the ventromedial and paraventricular nuclei of the hypothalamus*. (2) The same increase in blood glucose level simultaneously *decreases* the firing of *glucosensitive neurons* in the *hunger center of the lateral hypothalamus*. In addition, some amino acids and lipid substances affect the rates of firing of these same neurons or other closely associated neurons.

Temperature Regulation and Food Intake. When an animal is exposed to cold, it tends to increase feeding; when it is exposed to heat, it tends to decrease its caloric intake. This is caused by interaction within the hypothalamus between the temperature-regulating system (see Chapter 73) and the food intake–regulating system. This is important because increased food intake in a cold animal (1) increases its metabolic rate and (2) provides increased fat for insulation, both of which tend to correct the cold state.

Feedback Signals from Adipose Tissue Regulate Food Intake. Most of the stored energy in the body consists of fat, the amount of which can vary considerably in different individuals. What regulates this energy reserve, and why is there so much variability among individuals?

Studies in humans and in experimental animals indicate that the hypothalamus senses energy storage through the actions of *leptin*, a peptide hormone released from adipocytes. When the amount of adipose tissue increases (signaling excess energy storage), the adipocytes produce increased amounts of leptin, which is released into the blood. Leptin then circulates to the brain, where it moves across the blood-brain barrier by facilitated diffusion and occupies leptin receptors at multiple sites in the hypothalamus, especially the POMC neurons of the arcuate nuclei and neurons of the paraventricular nuclei.

Stimulation of leptin receptors in these hypothalamic nuclei initiates multiple actions that decrease fat storage, including (1) decreased production in the hypothalamus of appetite stimulators, such as *NPY* and *AGRP*; (2) *activation of POMC neurons*, causing release of α-MSH and activation of melanocortin receptors; (3) increased production in the hypothalamus of substances, such as *corticotropin-releasing hormone*, that decrease food intake; (4) *increased sympathetic nerve activity* (through neural projections from the hypothalamus to the vasomotor centers), which increases metabolic rate and energy expenditure; and (5) *decreased insulin secretion* by the pancreatic beta cells, which decreases energy storage. Thus, leptin is an important means by which the adipose tissue signals the brain that enough energy has been stored and that intake of food is no longer necessary.

In mice or humans with mutations that render their fat cells unable to produce leptin or mutations that cause defective leptin receptors in the hypothalamus, marked hyperphagia and morbid obesity occur. In most obese humans, however, there does not appear to be a deficiency of leptin production because plasma leptin levels increase in proportion with increasing adiposity. Therefore, some physiologists believe that obesity may be associated with *leptin resistance*; that is, leptin receptors or postreceptor signaling pathways normally activated by leptin may be defective in obese people, who continue to eat despite very high levels of leptin.

Another explanation for the failure of leptin to prevent increasing adiposity in obese individuals is that there are many redundant systems that control feeding behavior, as well as social and cultural factors that can cause continued excess food intake even in the presence of high levels of leptin.

Summary of Long-Term Regulation. Even though our information on the different feedback factors in long-term feeding regulation is imprecise, we can make the following general statement: When the energy stores of the body fall below normal, the feeding centers of the hypothalamus and other areas of the brain become highly active, and the person exhibits increased hunger, as well as searching for food. Conversely, when the energy stores (mainly the fat stores) are already abundant, the person usually loses the sensation of hunger and develops a state of satiety.

Importance of Having Both Long- and Short-Term Regulatory Systems for Feeding

The long-term regulatory system for feeding, which includes all the nutritional energy feedback mechanisms, helps maintain constant stores of nutrients in the tissues, preventing them from becoming too low or too high. The short-term regulatory stimuli serve two other purposes. First, they tend to make the person eat smaller quantities at each eating session, thus allowing food to pass through the gastrointestinal tract at a steadier pace so that its digestive and absorptive mechanisms can work at optimal rates rather than becoming periodically overburdened. Second, they help prevent the person from eating amounts at each meal that would be too much for the metabolic storage systems once all the food has been absorbed.

Obesity

Obesity can be defined as an excess of body fat. A surrogate marker for body fat content is the body mass index (BMI), which is calculated as:

BMI = Weight in kg/Height in m^2

In clinical terms, a BMI between 25 and 29.9 kg/m^2 is called overweight, and a BMI greater than 30 kg/m^2 is called obese. BMI is not a direct estimate of adiposity and does not take into account the fact that some individuals have a high BMI due to a large muscle mass. A better way to define obesity is to actually measure the percentage of total body fat. Obesity is usually defined as 25 percent or greater total body fat in men and 35 percent or greater in women. Although percentage of body fat can be estimated with various methods, such as measuring skin-fold thickness, bioelectrical impedance, or underwater weighing, these methods are rarely used in clinical practice, where BMI is commonly used to assess obesity.

The prevalence of obesity in children and adults in the United States and in many other industrialized countries is rapidly increasing, rising by more than 30 percent over the past decade. Approximately 65 percent of adults in the United States are overweight, and nearly 33 percent of adults are obese.

Obesity Results from Greater Energy Intake Than Energy Expenditure. When greater quantities of energy (in the form of food) enter the body than are expended, the body weight increases, and most of the excess energy is stored as fat. Therefore, excessive adiposity (obesity) is caused by energy intake in excess of energy output. For each 9.3 Calories of excess energy that enter the body, approximately 1 gram of fat is stored.

Fat is stored mainly in adipocytes in subcutaneous tissue and in the intraperitoneal cavity, although the liver and other tissues of the body often accumulate significant amounts of lipids in obese persons. The metabolic processes involved in fat storage were discussed in Chapter 68.

It was previously believed that the number of adipocytes could increase substantially only during infancy and childhood and that excess energy intake in children led to *hyperplastic obesity*, associated with increased numbers of adipocytes and only small increases in adipocyte size. In contrast, obesity developing in adults was thought to increase only adipocyte size, resulting in *hypertrophic obesity*. Recent studies, however, have shown that new adipocytes can differentiate from fibroblast-like preadipocytes at any period of life and that the development of obesity in adults is accompanied by increased numbers, as well as increased size, of adipocytes. An extremely obese person may have as many as four times as many adipocytes, each containing twice as much lipid, as a lean person.

Once a person has become obese and a stable weight is obtained, energy intake once again equals energy output. For a person to lose weight, energy intake must be *less* than energy expenditure.

Decreased Physical Activity and Abnormal Feeding Regulation as Causes of Obesity

The causes of obesity are complex. Although genes play an important role in programming the powerful physiological mechanisms that regulate food intake and energy metabolism, lifestyle and environmental factors may play the dominant role in many obese people. The rapid increase in the prevalence of obesity in the past 20 to 30 years emphasizes the important role of lifestyle and environmental factors because genetic changes could not have occurred so rapidly.

Sedentary Lifestyle Is a Major Cause of Obesity. Regular physical activity and physical training are known to increase muscle mass and decrease body fat mass, whereas inadequate physical activity is typically associated with decreased muscle mass and increased adiposity. For example, studies have shown a close association between sedentary behaviors, such as prolonged television watching, and obesity.

About 25 to 30 percent of the energy used each day by the average person goes into muscular activity, and in a laborer, as much as 60 to 70 percent is used in this way. In obese people, increased physical activity usually increases energy expenditure more than food intake, resulting in significant weight loss. Even a single episode of strenuous exercise may increase basal energy expenditure for several hours after the physical activity is stopped. Because muscular activity is by far the most important means by which energy is expended in the body, increased physical activity is often an effective means of reducing fat stores.

Abnormal Feeding Behavior Is an Important Cause of Obesity. Although powerful physiological mechanisms regulate food intake, there are also important environmental and psychological factors that can cause abnormal feeding behavior, excessive energy intake, and obesity.

Environmental, Social, and Psychological Factors Contribute to Abnormal Feeding. As discussed previously, the importance of environmental factors is evident from the rapid increase in the prevalence of obesity in most industrialized countries, which has coincided with an abundance of high-energy foods (especially fatty foods) and sedentary lifestyles.

Psychological factors may contribute to obesity in some people. For example, people often gain large amounts of weight during or after stressful situations, such as the death of a parent, a severe illness, or even mental depression. It seems that eating can be a means of releasing tension.

Childhood Overnutrition as a Possible Cause of Obesity. One factor that may contribute to obesity is the prevalent idea that healthy eating habits require three meals a day and that each meal must be filling. Many young children are forced into this habit by overly solicitous parents, and the children continue to practice it throughout life.

The rate of formation of new fat cells is especially rapid in the first few years of life, and the greater the rate of fat storage, the greater the number of fat cells. The number of fat cells in obese children is often as much as three times that in normal children. Therefore, it has been suggested that overnutrition of children—especially in infancy and, to a lesser extent, during the later years of childhood—can lead to a lifetime of obesity.

Neurogenic Abnormalities as a Cause of Obesity. We previously pointed out that lesions in the ventromedial nuclei of the hypothalamus cause an animal to eat excessively and become obese. People with hypophysial tumors that encroach on the hypothalamus often develop progressive obesity, demonstrating that obesity in human beings, too, can result from damage to the hypothalamus.

Although hypothalamic damage is almost never found in obese people, it is possible that the functional organization

of the hypothalamic or other neurogenic feeding centers in obese individuals is different from that in nonobese persons. Also, there may be abnormalities of neurotransmitters or receptor mechanisms in the neural pathways of the hypothalamus that control feeding. In support of this theory, an obese person who has reduced to normal weight by strict dietary measures usually develops intense hunger that is demonstrably far greater than that of a normal person. This indicates that the "set-point" of an obese person's feeding control system is at a much higher level of nutrient storage than that of a nonobese person.

Studies in experimental animals also indicate that when food intake is restricted in obese animals, there are marked neurotransmitter changes in the hypothalamus that greatly increase hunger and oppose weight loss. Some of these changes include increased formation of orexigenic neurotransmitters such as NPY and decreased formation of anorexic substances such as leptin and α-MSH.

Genetic Factors as a Cause of Obesity. Obesity definitely runs in families. Yet it has been difficult to determine the precise role of genetics in contributing to obesity because family members generally share many of the same eating habits and physical activity patterns. Current evidence, however, suggests that 20 to 25 percent of cases of obesity may be caused by genetic factors.

Genes can contribute to obesity by causing abnormalities of (1) one or more of the pathways that regulate the feeding centers and (2) energy expenditure and fat storage. Three of the monogenic (single-gene) causes of obesity are (1) *mutations of MCR-4*, the most common monogenic form of obesity discovered thus far; (2) *congenital leptin deficiency* caused by mutations of the leptin gene, which are very rare; and (3) *mutations of the leptin receptor*, also very rare. All these monogenic forms of obesity account for only a very small percentage of obesity. It is likely that many gene variations interact with environmental factors to influence the amount and distribution of body fat.

Treatment of Obesity

Treatment of obesity depends on decreasing energy input below energy expenditure and creating a sustained negative energy balance until the desired weight loss is achieved. In other words, this means either reducing energy intake or increasing energy expenditure. The current National Institutes of Health (NIH) guidelines recommend a decrease in caloric intake of 500 kilocalories per day for overweight and moderately obese persons (BMI > 25 but < 35 kg/m^2) to achieve a weight loss of approximately 1 pound each week. A more aggressive energy deficit of 500 to 1000 kilocalories per day is recommended for persons with BMIs greater than 35 kg/m^2. Typically, such an energy deficit, if it can be achieved and sustained, will cause a weight loss of about 1 to 2 pounds per week, or about a 10 percent weight loss after 6 months. For most people attempting to lose weight, increasing physical activity is also an important component of successful long-term weight loss.

To decrease energy intake, most reducing diets are designed to contain large quantities of "bulk," which is generally made up of non-nutritive cellulose substances. This bulk distends the stomach and thereby partially appeases hunger. In experimental animals, such a procedure simply makes the animal increase its food intake even more, but human beings can often fool themselves because their food intake is sometimes controlled as much by habit as by hunger. As pointed out later in connection with starvation, it is important to prevent vitamin deficiencies during the dieting period.

Various *drugs for decreasing the degree of hunger* have been used in the treatment of obesity. The most widely used drugs are *amphetamines* (or amphetamine derivatives), which directly inhibit the feeding centers in the brain. One drug for treating obesity is *sibutramine*, a sympathomimetic that reduces food intake and increases energy expenditure. The danger in using these drugs is that they simultaneously overexcite the sympathetic nervous system and raise the blood pressure. Also, a person soon adapts to the drug, so weight reduction is usually no greater than 5 to 10 percent.

Another group of drugs works by altering lipid metabolism. For example, *orlistat, a lipase inhibitor, reduces the intestinal digestion of fat*. This causes a portion of the ingested fat to be lost in the feces and therefore reduces energy absorption. However, fecal fat loss may cause unpleasant gastrointestinal side effects, as well as loss of fat-soluble vitamins in the feces.

Significant weight loss can be achieved in many obese persons with increased physical activity. The more exercise one gets, the greater the daily energy expenditure and the more rapidly the obesity disappears. Therefore, forced exercise is often an essential part of treatment. The current clinical guidelines for the treatment of obesity recommend that the first step be lifestyle modifications that include increased physical activity combined with a reduction in caloric intake. For morbidly obese patients with BMIs greater than 40, or for patients with BMIs greater than 35 and conditions such as hypertension or type II diabetes that predispose them to other serious diseases, various surgical procedures can be used to decrease the fat mass of the body or to decrease the amount of food that can be eaten at each meal.

Two of the most common surgical procedures used in the United States to treat morbid obesity are gastric bypass surgery and gastric banding surgery. *Gastric bypass surgery* involves construction of a small pouch in the proximal part of the stomach that is then connected to the jejunum with a section of small bowel of varying lengths; the pouch is separated from the remaining part of the stomach with staples. *Gastric banding surgery* involves placing an adjustable band around the stomach near its upper end; this also creates a small stomach pouch that restricts the amount of food that can be eaten at each meal. Although these surgical procedures generally produce substantial weight loss in obese patients, they are major operations, and their long-term effects on overall health and mortality are still uncertain.

Inanition, Anorexia, and Cachexia

Inanition is the opposite of obesity and is characterized by extreme weight loss. It can be caused by inadequate availability of food or by pathophysiological conditions that greatly decrease the desire for food, including psychogenic disturbances, hypothalamic abnormalities, and factors released from peripheral tissues. In many instances, especially in those with serious diseases such as cancer, the reduced desire for food may be associated with increased energy expenditure, causing serious weight loss.

Anorexia can be defined as *a reduction in food intake caused primarily by diminished appetite*, as opposed to the

literal definition of "not eating." This definition emphasizes the important role of central neural mechanisms in the pathophysiology of anorexia in diseases such as cancer, when other common problems, such as pain and nausea, may also cause a person to consume less food. *Anorexia nervosa* is an abnormal psychic state in which a person loses all desire for food and even becomes nauseated by food; as a result, severe inanition occurs.

Cachexia is a metabolic disorder of increased energy expenditure leading to weight loss greater than that caused by reduced food intake alone. Anorexia and cachexia often occur together in many types of cancer or in the "wasting syndrome" observed in patients with acquired immunodeficiency syndrome (AIDS) and chronic inflammatory disorders. Almost all types of cancer cause both anorexia and cachexia, and more than half of cancer patients develop anorexia-cachexia syndrome during the course of their disease.

Central neural and peripheral factors are believed to contribute to cancer-induced anorexia and cachexia. Several inflammatory cytokines, including *tumor necrosis factor-α, interleukin-6, interleukin-1β*, and a *proteolysis-inducing factor*, have been shown to cause anorexia and cachexia. Most of these inflammatory cytokines appear to mediate anorexia by activation of the *melanocortin system* in the hypothalamus. The precise mechanisms by which cytokines or tumor products interact with the melanocortin pathway to decrease food intake are still unclear, but blockade of the hypothalamic melanocortin receptors appears to almost completely prevent their anorexic and cachectic effects in experimental animals. Additional research, however, is necessary to better understand the pathophysiological mechanisms of anorexia and cachexia in cancer patients and to develop therapeutic agents to improve their nutritional status and survival.

Starvation

Depletion of Food Stores in the Body Tissues During Starvation. Even though the tissues preferentially use carbohydrate for energy over both fat and protein, the quantity of carbohydrate normally stored in the entire body is only a few hundred grams (mainly glycogen in the liver and muscles), and it can supply the energy required for body functions for perhaps half a day. Therefore, except for the first few hours of starvation, the major effects are progressive depletion of tissue fat and protein. Because fat is the prime source of energy (100 times as much fat energy is stored in the normal person as carbohydrate energy), the rate of fat depletion continues unabated, as shown in Figure 71-3, until most of the fat stores in the body are gone.

Protein undergoes three phases of depletion: rapid depletion at first, then greatly slowed depletion, and, finally, rapid depletion again shortly before death. The initial rapid depletion is caused by the use of easily mobilized protein for direct metabolism or for conversion to glucose and then metabolism of glucose mainly by the brain. After the readily mobilized protein stores have been depleted during the early phase of starvation, the remaining protein is not so easily removed. At this time, the rate of gluconeogenesis decreases to one-third to one-fifth its previous rate, and the rate of depletion of protein becomes greatly decreased. The lessened availability of glucose then initiates a series of events that leads to excessive fat utilization and conversion of some of the fat

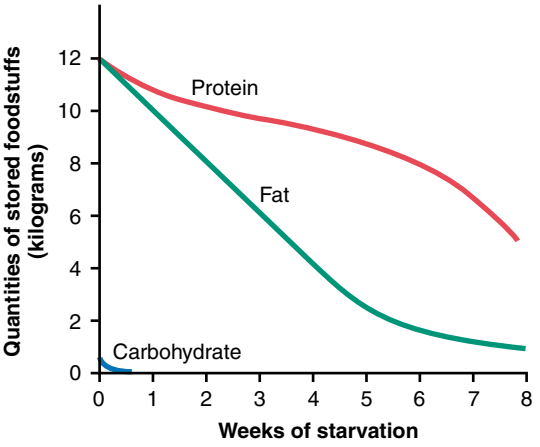


Figure 71-3 Effect of starvation on the food stores of the body.

breakdown products to ketone bodies, producing the state of *ketosis*, which is discussed in Chapter 68. The ketone bodies, like glucose, can cross the blood-brain barrier and can be used by the brain cells for energy. Therefore, about two thirds of the brain's energy is now derived from these ketone bodies, principally from beta-hydroxybutyrate. This sequence of events leads to at least partial preservation of the protein stores of the body.

There finally comes a time when the fat stores are almost depleted, and the only remaining source of energy is protein. At that time, the protein stores once again enter a stage of rapid depletion. Because proteins are also essential for the maintenance of cellular function, death ordinarily ensues when the proteins of the body have been depleted to about half their normal level.

Vitamin Deficiencies in Starvation. The stores of some of the vitamins, especially the water-soluble vitamins—the vitamin B group and vitamin C—do not last long during starvation. Consequently, after a week or more of starvation, mild vitamin deficiencies usually begin to appear, and after several weeks, severe vitamin deficiencies can occur. These deficiencies can add to the debility that leads to death.

Vitamins

Daily Requirements of Vitamins. A vitamin is an organic compound needed in small quantities for normal metabolism that cannot be manufactured in the cells of the body. Lack of vitamins in the diet can cause important metabolic deficits. Table 71-3 lists the amounts of important vitamins required daily by the average person. These requirements vary considerably, depending on such factors as body size, rate of growth, amount of exercise, and pregnancy.

Storage of Vitamins in the Body. Vitamins are stored to a slight extent in all cells. Some vitamins are stored to a major extent in the liver. For instance, the quantity of vitamin A stored in the liver may be sufficient to maintain a person for 5 to 10 months without any intake of vitamin A. The quantity of vitamin D stored in the liver is usually sufficient to maintain a person for 2 to 4 months without any additional intake of vitamin D.

The storage of most water-soluble vitamins is relatively slight. This applies especially to most vitamin B compounds. When a person's diet is deficient in vitamin B compounds,

Table 71-3 Required Daily Amounts of Vitamins

Vitamin	Amount
A	5000 IU
Thiamine	1.5 mg
Riboflavin	1.8 mg
Niacin	20 mg
Ascorbic acid	45 mg
D	400 IU
E	15 IU
K	70 µg
Folic acid	0.4 mg
B_{12}	3 µg
Pyridoxine	2 mg
Pantothenic acid	Unknown

clinical symptoms of the deficiency can sometimes be recognized within a few days (except for vitamin B_{12}, which can last in the liver in a bound form for a year or longer). Absence of vitamin C, another water-soluble vitamin, can cause symptoms within a few weeks and can cause death from scurvy in 20 to 30 weeks.

Vitamin A

Vitamin A occurs in animal tissues as *retinol*. This vitamin does not occur in foods of vegetable origin, but *provitamins* for the formation of vitamin A do occur in abundance in many vegetable foods. These are the yellow and red *carotenoid pigments*, which, because their chemical structures are similar to that of vitamin A, can be changed into vitamin A in the liver.

Vitamin A Deficiency Causes "Night Blindness" and Abnormal Epithelial Cell Growth. One basic function of vitamin A is its use in the formation of the retinal pigments of the eye, which is discussed in Chapter 50. Vitamin A is needed to form the visual pigments and, therefore, to prevent night blindness.

Vitamin A is also necessary for normal growth of most cells of the body and especially for normal growth and proliferation of the different types of epithelial cells. When vitamin A is lacking, the epithelial structures of the body tend to become stratified and keratinized. Vitamin A deficiency manifests itself by (1) scaliness of the skin and sometimes acne; (2) failure of growth of young animals, including cessation of skeletal growth; (3) failure of reproduction, associated especially with atrophy of the germinal epithelium of the testes and sometimes with interruption of the female sexual cycle; and (4) keratinization of the cornea, with resultant corneal opacity and blindness.

In vitamin A deficiency, the damaged epithelial structures often become infected (e.g., conjunctivae of the eyes, linings of the urinary tract, and respiratory passages). Vitamin A has been called an "anti-infection" vitamin.

Thiamine (Vitamin B_1)

Thiamine operates in the metabolic systems of the body principally as *thiamine pyrophosphate;* this compound functions as a *cocarboxylase*, operating mainly in conjunction with a protein decarboxylase for decarboxylation of pyruvic acid and other α-keto acids, as discussed in Chapter 67.

Thiamine deficiency *(beriberi)* causes decreased utilization of pyruvic acid and some amino acids by the tissues, but increased utilization of fats. Thus, thiamine is specifically needed for the final metabolism of carbohydrates and many amino acids. The decreased utilization of these nutrients is responsible for many debilities associated with thiamine deficiency.

Thiamine Deficiency Causes Lesions of the Central and Peripheral Nervous Systems. The central nervous system normally depends almost entirely on the metabolism of carbohydrates for its energy. In thiamine deficiency, the utilization of glucose by nervous tissue may be decreased 50 to 60 percent and is replaced by the utilization of ketone bodies derived from fat metabolism. The neuronal cells of the central nervous system frequently show chromatolysis and swelling during thiamine deficiency, changes that are characteristic of neuronal cells with poor nutrition. These changes can disrupt communication in many portions of the central nervous system.

Thiamine deficiency can cause *degeneration of myelin sheaths* of nerve fibers in both the peripheral nerves and the central nervous system. Lesions in the peripheral nerves frequently cause them to become extremely irritable, resulting in "polyneuritis," characterized by pain radiating along the course of one or many peripheral nerves. Also, fiber tracts in the cord can degenerate to such an extent that *paralysis* occasionally results; even in the absence of paralysis, the muscles atrophy, resulting in severe weakness.

Thiamine Deficiency Weakens the Heart and Causes Peripheral Vasodilation. A person with severe thiamine deficiency eventually develops *cardiac failure* because of weakened cardiac muscle. Further, the venous return of blood to the heart may be increased to as much as two times normal. This occurs because thiamine deficiency causes *peripheral vasodilation* throughout the circulatory system, presumably as a result of decreased release of metabolic energy in the tissues, leading to local vascular dilation. The cardiac effects of thiamine deficiency are due partly to high blood flow into the heart and partly to primary weakness of the cardiac muscle. *Peripheral edema* and *ascites* also occur to a major extent in some people with thiamine deficiency, mainly because of cardiac failure.

Thiamine Deficiency Causes Gastrointestinal Tract Disturbances. Among the gastrointestinal symptoms of thiamine deficiency are indigestion, severe constipation, anorexia, gastric atony, and hypochlorhydria. All these effects presumably result from failure of the smooth muscle and glands of the gastrointestinal tract to derive sufficient energy from carbohydrate metabolism.

The overall picture of thiamine deficiency, including polyneuritis, cardiovascular symptoms, and gastrointestinal disorders, is frequently referred to as *beriberi*—especially when the cardiovascular symptoms predominate.

Niacin

Niacin, also called *nicotinic acid*, functions in the body as coenzymes in the form of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are hydrogen acceptors; they combine with hydrogen atoms as they are removed from

food substrates by many types of dehydrogenases. The typical operation of both these coenzymes is presented in Chapter 67. When a deficiency of niacin exists, the normal rate of dehydrogenation cannot be maintained; therefore, oxidative delivery of energy from the foodstuffs to the functioning elements of all cells cannot occur at normal rates.

In the early stages of niacin deficiency, simple physiological changes such as muscle weakness and poor glandular secretion may occur, but in severe niacin deficiency, actual tissue death ensues. Pathological lesions appear in many parts of the central nervous system, and permanent dementia or many types of psychoses may result. Also, the skin develops a cracked, pigmented scaliness in areas that are exposed to mechanical irritation or sun irradiation; thus, it appears that in persons with niacin deficiency, the skin is unable to repair irritative damage.

Niacin deficiency causes intense irritation and inflammation of the mucous membranes of the mouth and other portions of the gastrointestinal tract, resulting in many digestive abnormalities that can lead to widespread gastrointestinal hemorrhage in severe cases. It is possible that this results from generalized depression of metabolism in the gastrointestinal epithelium and failure of appropriate epithelial repair.

The clinical entity called *pellagra* and the canine disease called *black tongue* are caused mainly by niacin deficiency. Pellagra is greatly exacerbated in people on a corn diet because corn is deficient in the amino acid tryptophan, which can be converted in limited quantities to niacin in the body.

Riboflavin (Vitamin B_2)

Riboflavin normally combines in the tissues with phosphoric acid to form two coenzymes, *flavin mononucleotide (FMN)* and *flavin adenine dinucleotide (FAD)*. They operate as hydrogen carriers in important oxidative systems of the mitochondria. NAD, operating in association with specific dehydrogenases, usually accepts hydrogen removed from various food substrates and then passes the hydrogen to FMN or FAD; finally, the hydrogen is released as an ion into the mitochondrial matrix to become oxidized by oxygen (described in Chapter 67).

Deficiency of riboflavin in experimental animals causes severe dermatitis, vomiting, diarrhea, muscle spasticity that finally becomes muscle weakness, coma and decline in body temperature, and then death. Thus, severe riboflavin deficiency can cause many of the same effects as a lack of niacin in the diet; presumably, the debilities that result in each instance are due to generally depressed oxidative processes within the cells.

In the human being, there are no known cases of riboflavin deficiency severe enough to cause the marked debilities noted in experimental animals, but mild riboflavin deficiency is probably common. Such deficiency causes digestive disturbances, burning sensations of the skin and eyes, cracking at the corners of the mouth, headaches, mental depression, forgetfulness, and so on.

Although the manifestations of riboflavin deficiency are usually relatively mild, this deficiency frequently occurs in association with deficiency of thiamine, niacin, or both. Many deficiency syndromes, including *pellagra, beriberi, sprue*, and *kwashiorkor*, are probably due to a combined deficiency of a number of vitamins, as well as other aspects of malnutrition.

Vitamin B_{12}

Several *cobalamin* compounds that possess the common prosthetic group shown next exhibit so-called vitamin B_{12} activity. Note that this prosthetic group contains cobalt, which has bonds similar to those of iron in the hemoglobin molecule. It is likely that the cobalt atom functions in much the same way that the iron atom functions to combine reversibly with other substances.

Vitamin B_{12} Deficiency Causes Pernicious Anemia. Vitamin B_{12} performs several metabolic functions, acting as a hydrogen acceptor coenzyme. Its most important function is to act as a coenzyme for reducing ribonucleotides to deoxyribonucleotides, a step that is necessary in the replication of genes. This could explain the major functions of vitamin B_{12}: (1) promotion of growth and (2) promotion of red blood cell formation and maturation. This red cell function is described in detail in Chapter 32 in relation to pernicious anemia, a type of anemia caused by failure of red blood cell maturation when vitamin B_{12} is deficient.

Vitamin B_{12} Deficiency Causes Demyelination of the Large Nerve Fibers of the Spinal Cord. The demyelination of nerve fibers in people with vitamin B_{12} deficiency occurs especially in the posterior columns, and occasionally the lateral columns, of the spinal cord. As a result, many people with pernicious anemia have loss of peripheral sensation and, in severe cases, even become paralyzed.

The usual cause of vitamin B_{12} deficiency is not lack of this vitamin in the food but deficiency of formation of *intrinsic factor*, which is normally secreted by the parietal cells of the gastric glands and is essential for absorption of vitamin B_{12} by the ileal mucosa. This is discussed in Chapters 32 and 66.

Folic Acid (Pteroylglutamic Acid)

Several pteroylglutamic acids exhibit the "folic acid effect." Folic acid functions as a carrier of hydroxymethyl and formyl groups. *Perhaps its most important use in the body is in the synthesis of purines and thymine, which are required for formation of DNA*. Therefore, folic acid, like vitamin B_{12}, is required for replication of the cellular genes. This may explain one of the most important functions of folic acid—to promote growth. Indeed, when it is absent from the diet, an animal grows very little.

Folic acid is an even more potent growth promoter than vitamin B_{12} and, like vitamin B_{12}, is important for the maturation of red blood cells, as discussed in Chapter 32. However, vitamin B_{12} and folic acid each perform specific and different chemical functions in promoting growth and maturation of red blood cells. One of the significant effects of folic acid deficiency is the development of *macrocytic anemia*, almost identical to that which occurs in pernicious anemia. This often can be treated effectively with folic acid alone.

Pyridoxine (Vitamin B_6)

Pyridoxine exists in the form of *pyridoxal phosphate* in the cells and functions as a coenzyme for many chemical reactions related to amino acid and protein metabolism. *Its most important role is that of coenzyme in the transamination process for the synthesis of amino acids*. As a result, pyridoxine plays many key roles in metabolism, especially protein metabolism. Also, it is believed to act in the transport of some amino acids across cell membranes.

Dietary lack of pyridoxine in lower animals can cause dermatitis, decreased rate of growth, development of fatty

liver, anemia, and evidence of mental deterioration. Rarely, in children, pyridoxine deficiency has been known to cause seizures, dermatitis, and gastrointestinal disturbances such as nausea and vomiting.

Pantothenic Acid

Pantothenic acid is mainly incorporated in the body into *coenzyme A (CoA)*, which has many metabolic roles in the cells. Two of these discussed at length in Chapters 67 and 68 are (1) conversion of decarboxylated pyruvic acid into acetyl-CoA before its entry into the citric acid cycle and (2) degradation of fatty acid molecules into multiple molecules of acetyl-CoA. *Thus, lack of pantothenic acid can lead to depressed metabolism of both carbohydrates and fats.*

Deficiency of pantothenic acid in lower animals can cause retarded growth, failure of reproduction, graying of the hair, dermatitis, fatty liver, and hemorrhagic adrenocortical necrosis. In the human being, no definite deficiency syndrome has been proved, presumably because of the wide occurrence of this vitamin in almost all foods and because small amounts can probably be synthesized in the body. This does not mean that pantothenic acid is not of value in the metabolic systems of the body; indeed, it is perhaps as necessary as any other vitamin.

Ascorbic Acid (Vitamin C)

Ascorbic Acid Deficiency Weakens Collagen Fibers Throughout the Body. Ascorbic acid is essential for activating the enzyme *prolyl hydroxylase*, which promotes the hydroxylation step in the formation of hydroxyproline, an integral constituent of collagen. Without ascorbic acid, the collagen fibers that are formed in virtually all tissues of the body are defective and weak. Therefore, this vitamin is essential for the growth and strength of the fibers in subcutaneous tissue, cartilage, bone, and teeth.

Ascorbic Acid Deficiency Causes Scurvy. Deficiency of ascorbic acid for 20 to 30 weeks, which occurred frequently during long ship voyages in the past, causes *scurvy*. One of the most important effects of scurvy is *failure of wounds to heal*. This is caused by failure of the cells to deposit collagen fibrils and intercellular cement substances. As a result, healing of a wound may require several months instead of the several days ordinarily necessary.

Lack of ascorbic acid also causes *cessation of bone growth*. The cells of the growing epiphyses continue to proliferate, but no new collagen is laid down between the cells, and the bones fracture easily at the point of growth because of failure to ossify. Also, when an already ossified bone fractures in a person with ascorbic acid deficiency, the osteoblasts cannot form new bone matrix. Consequently, the fractured bone does not heal.

The *blood vessel walls become extremely fragile* in scurvy because of (1) failure of the endothelial cells to be cemented together properly and (2) failure to form the collagen fibrils normally present in vessel walls. The capillaries are especially likely to rupture, and as a result, many small petechial hemorrhages occur throughout the body. The hemorrhages beneath the skin cause purpuric blotches, sometimes over the entire body. To test for ascorbic acid deficiency, one can produce such petechial hemorrhages by inflating a blood pressure cuff over the upper arm; this occludes the venous return of blood, the capillary pressure rises, and red blotches occur on the forearm if the ascorbic acid deficiency is sufficiently severe.

In extreme scurvy, the muscle cells sometimes fragment; lesions of the gums occur, with loosening of the teeth; infections of the mouth develop; and vomiting of blood, bloody stools, and cerebral hemorrhage can all occur. Finally, high fever often develops before death.

Vitamin D

Vitamin D increases calcium absorption from the gastrointestinal tract and helps control calcium deposition in the bone. The mechanism by which vitamin D increases calcium absorption is mainly to promote active transport of calcium through the epithelium of the ileum. In particular, it increases the formation of a calcium-binding protein in the intestinal epithelial cells that aids in calcium absorption. The specific functions of vitamin D in relation to overall body calcium metabolism and bone formation are presented in Chapter 79.

Vitamin E

Several related compounds exhibit so-called vitamin E activity. Only rare instances of proved vitamin E deficiency have occurred in human beings. In experimental animals, lack of vitamin E can cause degeneration of the germinal epithelium in the testis and, therefore, can cause male sterility. Lack of vitamin E can also cause resorption of a fetus after conception in the female. Because of these effects of vitamin E deficiency, vitamin E is sometimes called the "antisterility vitamin." Deficiency of vitamin E prevents normal growth and sometimes causes degeneration of the renal tubular cells and the muscle cells.

Vitamin E is believed to play a protective role in the prevention of oxidation of unsaturated fats. In the absence of vitamin E, the quantity of unsaturated fats in the cells becomes diminished, causing abnormal structure and function of such cellular organelles as the mitochondria, the lysosomes, and even the cell membrane.

Vitamin K

Vitamin K is an essential co-factor to a liver enzyme that adds a carboxyl group to factors II (prothrombin), VII (proconvertin), IX, and X, all of which are important in blood coagulation. Without this carboxylation these coagulation factors are inactive. Therefore, when vitamin K deficiency occurs, blood clotting is retarded. The function of this vitamin and its relation to some of the anticoagulants, such as dicumarol, are presented in greater detail in Chapter 36.

Several compounds, both natural and synthetic, exhibit vitamin K activity. Because vitamin K is synthesized by bacteria in the colon, it is rare for a person to have a bleeding tendency because of vitamin K deficiency in the diet. However, when the bacteria of the colon are destroyed by the administration of large quantities of antibiotic drugs, vitamin K deficiency occurs rapidly because of the paucity of this compound in the normal diet.

Mineral Metabolism

The functions of many of the minerals, such as sodium, potassium, and chloride, are presented at appropriate points in the text. Only specific functions of minerals not covered elsewhere are mentioned here. The body content of the most important minerals is listed in Table 71-4, and the daily requirements of these are given in Table 71-5.

Table 71-4 Average Content of a 70-Kilogram Man

Constituent	Amount (grams)
Water	41,400
Fat	12,600
Protein	12,600
Carbohydrate	300
Sodium	63
Potassium	150
Calcium	1,160
Magnesium	21
Chloride	85
Phosphorus	670
Sulfur	112
Iron	3
Iodine	0.014

Table 71-5 Average Required Daily Amounts of Minerals for Adults

Mineral	Amount
Sodium	3.0 g
Potassium	1.0 g
Chloride	3.5 g
Calcium	1.2 g
Phosphorus	1.2 g
Iron	18.0 mg
Iodine	150.0 µg
Magnesium	0.4 g
Cobalt	Unknown
Copper	Unknown
Manganese	Unknown
Zinc	15 mg

Magnesium. Magnesium is about one sixth as plentiful in cells as potassium. Magnesium is required as a catalyst for many intracellular enzymatic reactions, particularly those related to carbohydrate metabolism.

The extracellular fluid magnesium concentration is slight, only 1.8 to 2.5 mEq/L. Increased extracellular concentration of magnesium depresses nervous system activity, as well as skeletal muscle contraction. This latter effect can be blocked by the administration of calcium. Low magnesium concentration causes increased irritability of the nervous system, peripheral vasodilation, and cardiac arrhythmias, especially after acute myocardial infarction.

Calcium. Calcium is present in the body mainly in the form of calcium phosphate in the bone. This subject is discussed in detail in Chapter 79, as is the calcium content of extracellular fluid. Excess quantities of calcium ions in extracellular fluid can cause the heart to stop in systole and can act as a mental depressant. At the other extreme, low levels of calcium can cause spontaneous discharge of nerve fibers, resulting in tetany, as discussed in Chapter 79.

Phosphorus. *Phosphate is the major anion of intracellular fluid.* Phosphates have the ability to combine reversibly with many coenzyme systems and with multiple other compounds that are necessary for the operation of metabolic processes. Many important reactions of phosphates have been catalogued at other points in this text, especially in relation to the functions of adenosine triphosphate, adenosine diphosphate, phosphocreatine, and so forth. Also, bone contains a tremendous amount of calcium phosphate, which is discussed in Chapter 79.

Iron. The function of iron in the body, especially in relation to the formation of hemoglobin, is discussed in Chapter 32. *Two thirds of the iron in the body is in the form of hemoglobin*, although smaller quantities are present in other forms, especially in the liver and the bone marrow. Electron carriers containing iron (especially the cytochromes) are present in the mitochondria of all cells of the body and are essential for most of the oxidation that occurs in the cells. Therefore, iron is absolutely essential for both the transport of oxygen to the tissues and the operation of oxidative systems within the tissue cells, without which life would cease within a few seconds.

Important Trace Elements in the Body. A few elements are present in the body in such small quantities that they are called *trace elements*. The amounts of these elements in foods are also usually minute. Yet without any one of them, a specific deficiency syndrome is likely to develop. Three of the most important are iodine, zinc, and fluorine.

Iodine. The best known of the trace elements is iodine. This element is discussed in Chapter 76 in connection with the formation and function of thyroid hormone; as shown in Table 71-4, the entire body contains an average of only 14 milligrams. Iodine is essential for the formation of *thyroxine* and *triiodothyronine*, the two thyroid hormones that are essential for maintenance of normal metabolic rates in all cells of the body.

Zinc. Zinc is an integral part of many enzymes, one of the most important of which is *carbonic anhydrase*, present in especially high concentration in the red blood cells. This enzyme is responsible for rapid combination of carbon dioxide with water in the red blood cells of the peripheral capillary blood and for rapid release of carbon dioxide from the pulmonary capillary blood into the alveoli. Carbonic anhydrase is also present to a major extent in the gastrointestinal mucosa, the tubules of the kidney, and the epithelial cells of many glands of the body. Consequently, zinc in small quantities is essential for the performance of many reactions related to carbon dioxide metabolism.

Zinc is also a component of *lactic dehydrogenase* and is therefore important for the interconversions between pyruvic acid and lactic acid. Finally, zinc is a component of some *peptidases* and is important for the digestion of proteins in the gastrointestinal tract.

Fluorine. Fluorine does not seem to be a necessary element for metabolism, but the presence of a small quantity of fluorine in the body during the period of life when the teeth are being formed subsequently protects against caries. Fluorine does not make the teeth stronger but has a poorly understood effect in suppressing the cariogenic process. It has been suggested that fluorine is deposited in the hydroxyapatite crystals of the tooth enamel and combines with and

therefore blocks the functions of various trace metals that are necessary for activation of the bacterial enzymes that cause caries. Therefore, when fluorine is present, the enzymes remain inactive and cause no caries.

Excessive intake of fluorine causes *fluorosis*, which manifests in its mild state by mottled teeth and in its more severe state by enlarged bones. It has been postulated that in this condition, fluorine combines with trace metals in some of the metabolic enzymes, including the phosphatases, so that various metabolic systems become partially inactivated. According to this theory, the mottled teeth and enlarged bones are due to abnormal enzyme systems in the odontoblasts and osteoblasts. Even though the mottled teeth are highly resistant to the development of caries, the structural strength of these teeth may be considerably lessened by the mottling process.

Bibliography

Bray GA: Lifestyle and pharmacological approaches to weight loss: efficacy and safety, *J Clin Endocrinol Metab* 93(11 Suppl 1):S81, 2008.

Coll AP: Effects of pro-opiomelanocortin (POMC) on food intake and body weight: mechanisms and therapeutic potential?, *Clin Sci (Lond)* 113:171, 2007.

Cone RD: Studies on the physiological functions of the melanocortin system, *Endocr Rev* 27:736, 2006.

da Silva AA, Kuo JJ, Hall JE: Role of hypothalamic melanocortin 3/4-receptors in mediating chronic cardiovascular, renal, and metabolic actions of leptin, *Hypertension* 43:1312, 2004.

Davy KP, Hall JE: Obesity and hypertension: two epidemics or one?, *Am J Physiol Regul Integr Comp Physiol* 286:R803, 2004.

Farooqi IS, O'Rahilly S: Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity, *Nat Clin Pract Endocrinol Metab* 4:569, 2008.

Friedman JM, Halaas JL: Leptin and the regulation of body weight in mammals, *Nature* 395:763, 1998.

Gao Q, Horvath TL: Cross-talk between estrogen and leptin signaling in the hypothalamus, *Am J Physiol Endocrinol Metab* 294(5):E817, 2008.

Hall JE: The kidney, hypertension, and obesity, *Hypertension* 4:625, 2003.

Hall JE, Henegar JR, Dwyer TM, et al: Is obesity a major cause of chronic kidney disease? *Adv Ren Replace Ther* 11:41, 2004.

Hall JE, Jones DW: What can we do about the "epidemic" of obesity, *Am J Hypertens* 15:657, 2002.

Holst JJ: The physiology of glucagon-like peptide 1, *Physiol Rev* 87:1409, 2007.

Jones G, Strugnell SA, DeLuca HF: Current understanding of the molecular actions of vitamin D, *Physiol Rev* 78:1193, 1998.

Laviano A, Inui A, Marks DL, et al: Neural control of the anorexia-cachexia syndrome, *Am J Physiol Endocrinol Metab* 295:E1000, 2008.

Lucock M: Is folic acid the ultimate functional food component for disease prevention?, *BMJ* 328:211, 2004.

Marty N, Dallaporta M, Thorens B: Brain glucose sensing, counterregulation, and energy homeostasis, *Physiology (Bethesda)* 22:241, 2007.

Morton GJ, Cummings DE, Baskin DG, et al: Central nervous system control of food intake and body weight, *Nature* 443:289, 2006.

National Institutes of Health: *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report*, Bethesda MD, 1998, National Heart, Lung, and Blood Institute and National Institute of Diabetes and Digestive and Kidney Diseases. Available at: http://www.nhlbi.nih.gov/guidelines/index.htm.

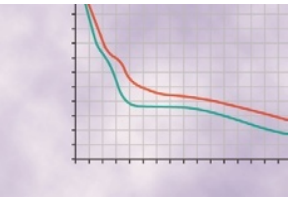
Powers HJ: Riboflavin (vitamin B_2) and health, *Am J Clin Nutr* 77:1352, 2003.

Tallam LS, da Silva AA, Hall JE: Melanocortin-4 receptor mediates chronic cardiovascular and metabolic actions of leptin, *Hypertension* 48:58, 2006.

Woods SC, D'Alessio DA: Central control of body weight and appetite, *J Clin Endocrinol Metab* 93(11 Suppl 1):S37, 2008.

CHAPTER 72

Energetics and Metabolic Rate



Adenosine Triphosphate (ATP) Functions as an "Energy Currency" in Metabolism

Carbohydrates, fats, and proteins can all be used by cells to synthesize large quantities of adenosine triphosphate (ATP), which can be used as an energy source for almost all other cellular functions. For this reason, ATP has been called an energy "currency" in cell metabolism. Indeed, the transfer of energy from foodstuffs to most functional systems of the cells can be done only through this medium of ATP (or the similar nucleotide guanosine triphosphate, GTP). Many of the attributes of ATP are presented in Chapter 2.

An attribute of ATP that makes it highly valuable as an energy currency is the large quantity of free energy (about 7300 calories, or 7.3 Calories [kilocalories], per mole under standard conditions, but as much as 12,000 calories under physiological conditions) vested in each of its two high-energy phosphate bonds. The amount of energy in each bond, when liberated by decomposition of ATP, is enough to cause almost any step of any chemical reaction in the body to take place if appropriate energy transfer is achieved. Some chemical reactions that require ATP energy use only a few hundred of the available 12,000 calories, and the remainder of this energy is lost in the form of heat.

ATP Is Generated by Combustion of Carbohydrates, Fats, and Proteins. In previous chapters, we discussed the transfer of energy from various foods to ATP. To summarize, ATP is produced from the following processes:

1. *Combustion of carbohydrates*—mainly glucose, but also smaller amounts of other sugars such as fructose; this occurs in the cytoplasm of the cell through the anaerobic process of *glycolysis* and in the cell mitochondria through the aerobic *citric acid (Krebs) cycle*.
2. *Combustion of fatty acids* in the cell mitochondria by *beta-oxidation*.
3. *Combustion of proteins*, which requires hydrolysis to their component amino acids and degradation of the amino acids to intermediate compounds of the citric acid cycle and then to acetyl coenzyme A and carbon dioxide.

ATP Energizes the Synthesis of Cellular Components. Among the most important intracellular processes that require ATP energy is the formation of peptide linkages between amino acids during the synthesis of proteins. The different peptide linkages, depending on which types of amino acids are linked, require from 500 to 5000 calories of energy per mole. From the discussion of protein synthesis in Chapter 3 recall that four high-energy phosphate bonds are expended during the cascade of reactions required to form each peptide linkage. This provides a total of 48,000 calories of energy, which is far more than the 500 to 5000 calories eventually stored in each of the peptide linkages.

ATP energy is also used in the synthesis of glucose from lactic acid and in the synthesis of fatty acids from acetyl coenzyme A. In addition, ATP energy is used for the synthesis of cholesterol, phospholipids, the hormones, and almost all other substances of the body. Even the urea excreted by the kidneys requires ATP for its formation from ammonia. One might wonder why energy is expended to form urea, which is simply discarded by the body. However, remembering the extreme toxicity of ammonia in the body fluids, one can see the value of this reaction, which keeps the ammonia concentration of the body fluids at a low level.

ATP Energizes Muscle Contraction. Muscle contraction will not occur without energy from ATP. Myosin, one of the important contractile proteins of the muscle fiber, acts as an enzyme to cause breakdown of ATP into adenosine diphosphate (ADP), thus releasing the energy required to cause contraction. Only a small amount of ATP is normally degraded in muscles when muscle contraction is not occurring, but this rate of ATP usage can rise to at least 150 times the resting level during short bursts of maximal contraction. The mechanism by which ATP energy is used to cause muscle contraction is discussed in Chapter 6.

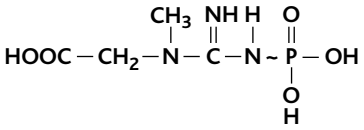
ATP Energizes Active Transport Across Membranes. In Chapters 4, 27, and 65, active transport of electrolytes and various nutrients across cell membranes and from the renal tubules and gastrointestinal tract into the blood is discussed. We noted that active transport of most electrolytes and substances such as glucose, amino acids, and acetoacetate can occur against an electrochemical gradient, even though the natural diffusion of the substances would be in the opposite direction. To oppose the electrochemical gradient requires energy, which is provided by ATP.

ATP Energizes Glandular Secretion. The same principles apply to glandular secretion as to the absorption of substances against concentration gradients because energy is required to concentrate substances as they are secreted by the glandular cells. In addition, energy is required to synthesize the organic compounds to be secreted.

ATP Energizes Nerve Conduction. The energy used during propagation of a nerve impulse is derived from the potential energy stored in the form of concentration differences of ions across the membranes. That is, a high concentration of potassium inside the fiber and a low concentration outside the fiber constitute a type of energy storage. Likewise, a high concentration of sodium on the outside of the membrane and a low concentration on the inside represent another store of energy. The energy needed to pass each action potential along the fiber membrane is derived from this energy storage, with small amounts of potassium transferring out of the cell and sodium into the cell during each of the action potentials. However, active transport systems energized by ATP then retransport the ions back through the membrane to their former positions.

Phosphocreatine Functions as an Accessory Storage Depot for Energy and as an "ATP Buffer"

Despite the paramount importance of ATP as a coupling agent for energy transfer, this substance is not the most abundant store of high-energy phosphate bonds in the cells. *Phosphocreatine*, which also contains high-energy phosphate bonds, is three to eight times more abundant than ATP. Also, the high-energy bond (~) of phosphocreatine contains about 8500 calories per mole under standard conditions and as many as 13,000 calories per mole under conditions in the body (37 °C and low concentrations of the reactants). This is slightly greater than the 12,000 calories per mole in each of the two high-energy phosphate bonds of ATP. The formula for creatinine phosphate is the following:



Unlike ATP, phosphocreatine cannot act as a direct coupling agent for energy transfer between the foods and the functional cellular systems, but it can transfer energy interchangeably with ATP. When extra amounts of ATP are available in the cell, much of its energy is used to synthesize phosphocreatine, thus building up this storehouse of energy. Then, when the ATP begins to be used up, the energy in the phosphocreatine is transferred rapidly back to ATP and then to the functional systems of the cells. This reversible interrelation between ATP and phosphocreatine is demonstrated by the following equation:

$$\text{Phosphocreatine} + \text{ADP} \;\downarrow\uparrow\; \text{ATP} + \text{Creatine}$$

Note that the higher energy level of the high-energy phosphate bond in phosphocreatine (1000 to 1500 calories per mole greater than that in ATP) causes the reaction between phosphocreatine and ADP to proceed rapidly toward the formation of new ATP every time even the slightest amount of ATP expends its energy elsewhere. Therefore, the slightest usage of ATP by the cells calls forth the energy from the phosphocreatine to synthesize new ATP. This effect keeps the concentration of ATP at an almost constant high level as long as any phosphocreatine remains. For this reason, we can call the ATP-phosphocreatine system an ATP "buffer" system. One can readily understand the importance of keeping the concentration of ATP nearly constant because the rates of almost all the metabolic reactions in the body depend on this constancy.

Anaerobic Versus Aerobic Energy

Anaerobic energy means energy that can be derived from foods without the simultaneous utilization of oxygen; *aerobic energy* means energy that can be derived from foods only by oxidative metabolism. In the discussions in Chapters 67 through 69, we noted that carbohydrates, fats, and proteins can all be oxidized to cause synthesis of ATP. However, *carbohydrates are the only significant foods that can be used to provide energy without the utilization of oxygen*; this energy release occurs during glycolytic breakdown of glucose or glycogen to pyruvic acid. For each mole of glucose that is split into pyruvic acid, 2 moles of ATP are formed. However, when stored glycogen in a cell is split to pyruvic acid, each mole of glucose in the glycogen gives rise to 3 moles of ATP. The reason for this difference is that free glucose entering the cell must be phosphorylated by using 1 mole of ATP before it can begin to be split; this is not true of glucose derived from glycogen because it comes from the glycogen already in the phosphorylated state, without the additional expenditure of ATP. *Thus, the best source of energy under anaerobic conditions is the stored glycogen of the cells.*

Anaerobic Energy Utilization During Hypoxia. One of the prime examples of anaerobic energy utilization occurs in acute hypoxia. When a person stops breathing, there is already a small amount of oxygen stored in the lungs and an additional amount stored in the hemoglobin of the blood. This oxygen is sufficient to keep the metabolic processes functioning for only about 2 minutes. Continued life beyond this time requires an additional source of energy. This can be derived for another minute or so from glycolysis—that is, the glycogen of the cells splitting into pyruvic acid, and the pyruvic acid becoming lactic acid, which diffuses out of the cells, as described in Chapter 67.

Anaerobic Energy Utilization During Strenuous Bursts of Activity Is Derived Mainly from Glycolysis. Skeletal muscles can perform extreme feats of strength for a few seconds but are much less capable during prolonged activity. Most of the extra energy required during these bursts of activity cannot come from the oxidative processes because they are too slow to respond. Instead, the extra energy comes from anaerobic sources: (1) ATP already present in the muscle cells, (2) phosphocreatine in the cells, and (3) anaerobic energy released by glycolytic breakdown of glycogen to lactic acid.

The maximum amount of ATP in muscle is only about 5 mmol/L of intracellular fluid, and this amount can maintain maximum muscle contraction for no more than a second or so. The amount of phosphocreatine in the cells is three to eight times this amount, but even by using all the phosphocreatine, maximum contraction can be maintained for only 5 to 10 seconds.

Release of energy by glycolysis can occur much more rapidly than can oxidative release of energy. Consequently, most of the extra energy required during strenuous activity that lasts for more than 5 to 10 seconds but less than 1 to 2 minutes is derived from anaerobic glycolysis. As a result, the glycogen content of muscles during strenuous bouts of exercise is reduced, whereas the lactic acid concentration of the blood rises. After the exercise is over, oxidative metabolism is used to reconvert about four fifths of the lactic acid into glucose;

the remainder becomes pyruvic acid and is degraded and oxidized in the citric acid cycle. The reconversion to glucose occurs principally in the liver cells, and the glucose is then transported in the blood back to the muscles, where it is stored once more in the form of glycogen.

Extra Consumption of Oxygen Repays the Oxygen Debt After Completion of Strenuous Exercise. After a period of strenuous exercise, a person continues to breathe hard and to consume large amounts of oxygen for at least a few minutes and sometimes for as long as 1 hour thereafter. This additional oxygen is used (1) to reconvert the lactic acid that has accumulated during exercise back into glucose, (2) to reconvert adenosine monophosphate and ADP to ATP, (3) to reconvert creatine and phosphate to phosphocreatine, (4) to re-establish normal concentrations of oxygen bound with hemoglobin and myoglobin, and (5) to raise the concentration of oxygen in the lungs to its normal level. This extra consumption of oxygen after exercise is called *repaying the oxygen debt*.

The principle of oxygen debt is discussed further in Chapter 84 in relation to sports physiology; the ability of a person to build up an oxygen debt is especially important in many types of athletics.

Summary of Energy Utilization by the Cells

With the background of the past few chapters and of the preceding discussion, we can now synthesize a composite picture of overall energy utilization by the cells, as shown in Figure 72-1. This figure demonstrates the anaerobic utilization of glycogen and glucose to form ATP and the aerobic utilization of compounds derived from carbohydrates, fats, proteins, and other substances to form additional ATP. In turn, ATP is in reversible equilibrium with phosphocreatine in the cells, and because larger quantities of phosphocreatine are present in the cells than ATP, much of the cells' stored energy is in this energy storehouse.

Energy from ATP can be used by the different functioning systems of the cells to provide for synthesis and growth, muscle contraction, glandular secretion, nerve impulse conduction, active absorption, and other cellular activities. If greater amounts of energy are demanded for cellular activities than can be provided by oxidative metabolism, the phosphocreatine storehouse is used first, and then anaerobic breakdown of glycogen follows rapidly. Thus, oxidative metabolism cannot deliver bursts of extreme energy to the cells nearly as rapidly as the anaerobic processes can, but at slower rates of usage, the oxidative processes can continue as long as energy stores (mainly fat) exist.

Control of Energy Release in the Cell

Rate Control of Enzyme-Catalyzed Reactions. Before discussing the control of energy release in the cell, it is necessary to consider the basic principles of *rate control* of enzymatically catalyzed chemical reactions, which are the types of reactions that occur almost universally throughout the body.

The mechanism by which an enzyme catalyzes a chemical reaction is for the enzyme first to combine loosely with one of the substrates of the reaction. This alters the bonding forces on the substrate sufficiently so that it can react with other substances. Therefore, the rate of the overall chemical reaction is determined by both the concentration of the enzyme and the concentration of the substrate that binds with the enzyme. The basic equation expressing this concept is as follows:

$$\text{Rate of reaction} = \frac{K_1 \times [\text{Enzyme}] \times [\text{Substrate}]}{K_2 + [\text{Substrate}]}$$

This is called the *Michaelis-Menten equation*. Figure 72-2 shows the application of this equation.

Role of Enzyme Concentration in Regulation of Metabolic Reactions. Figure 72-2 shows that *when the substrate concentration is high*, as shown in the right half of the figure, the rate of a chemical reaction is determined almost entirely by the concentration of the enzyme. Thus, as the enzyme concentration increases from an arbitrary value of 1 up to 2, 4, or 8, the rate of the reaction increases proportionately, as demonstrated by the rising levels of the curves. As an example, when large quantities of glucose enter the renal tubules in a person with diabetes mellitus—that is, the substrate glucose is in great excess in the tubules—further increases in tubular glucose have little effect on glucose reabsorption, because the transport enzymes are saturated. Under these conditions, the rate of reabsorption of the glucose is limited by the concentration of the transport enzymes in the proximal tubular cells, not by the concentration of the glucose itself.

Role of Substrate Concentration in Regulation of Metabolic Reactions. Note also in Figure 72-2 that when the substrate

Figure 72-1 Overall schema of energy transfer from foods to the adenylic acid system and then to the functional elements of the cells. (Modified from Soskin S, Levine R: Carbohydrate Metabolism. Chicago: University of Chicago Press, 1952.)

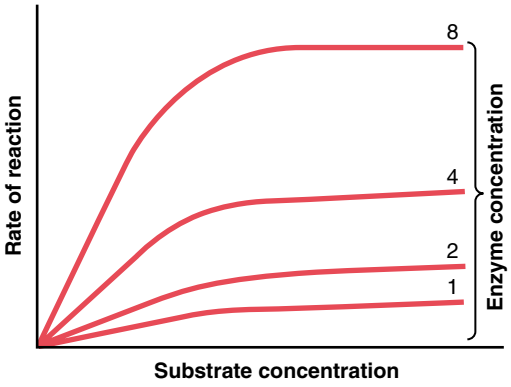


Figure 72-2 Effect of substrate and enzyme concentrations on the rate of enzyme-catalyzed reaction.

concentration becomes low enough that only a small portion of the enzyme is required in the reaction, the rate of the reaction becomes directly proportional to the substrate concentration, as well as the enzyme concentration. This is the relationship seen in the absorption of substances from the intestinal tract and renal tubules when their concentrations are low.

Rate Limitation in a Series of Reactions. Almost all chemical reactions of the body occur in series, with the product of one reaction acting as a substrate for the next reaction, and so on. Therefore, the overall rate of a complex series of chemical reactions is determined mainly by the rate of reaction of the slowest step in the series. This is called the *rate-limiting step* in the entire series.

ADP Concentration as a Rate-Controlling Factor in Energy Release. Under *resting* conditions, the concentration of ADP in the cells is extremely slight, so the chemical reactions that depend on ADP as one of the substrates are quite slow. They include all the oxidative metabolic pathways that release energy from food, as well as essentially all other pathways for the release of energy in the body. Thus, *ADP is a major rate-limiting factor* for almost all energy metabolism of the body.

When the cells become active, regardless of the type of activity, ATP is converted into ADP, increasing the concentration of ADP in direct proportion to the degree of activity of the cell. This ADP then automatically increases the rates of all the reactions for the metabolic release of energy from food. Thus, by this simple process, the amount of energy released in the cell is controlled by the degree of activity of the cell. In the absence of cellular activity, the release of energy stops because all the ADP soon becomes ATP.

Metabolic Rate

The *metabolism* of the body simply means all the chemical reactions in all the cells of the body, and the *metabolic rate* is normally expressed in terms of the rate of heat liberation during chemical reactions.

Heat Is the End Product of Almost All the Energy Released in the Body. In discussing many of the metabolic reactions in the preceding chapters, we noted that not all the energy in foods is transferred to ATP; instead, a large portion of this energy becomes heat. On average, 35 percent of the energy in foods becomes heat during ATP formation. Then, still more energy becomes heat as it is transferred from ATP to the functional systems of the cells, so even under optimal conditions, no more than 27 percent of all the energy from food is finally used by the functional systems.

Even when 27 percent of the energy reaches the functional systems of the cells, most of this eventually becomes heat. For example, when proteins are synthesized, large portions of ATP are used to form the peptide linkages and this stores energy in these linkages. But there is also continuous turnover of proteins—some being degraded while others are being formed. When proteins are degraded, the energy stored in the peptide linkages is released in the form of heat into the body.

Another example is the energy used for muscle activity. Much of this energy simply overcomes the viscosity of the muscles themselves or of the tissues so that the limbs can move. This viscous movement causes friction within the tissues, which generates heat.

Consider also the energy expended by the heart in pumping blood. The blood distends the arterial system, and this distention itself represents a reservoir of potential energy. As the blood flows through the peripheral vessels, the friction of the different layers of blood flowing over one another and the friction of the blood against the walls of the vessels turn all this energy into heat.

Essentially all the energy expended by the body is eventually converted into heat. The only significant exception occurs when the muscles are used to perform some form of work outside the body. For instance, when the muscles elevate an object to a height or propel the body up steps, a type of potential energy is created by raising a mass against gravity. But when external expenditure of energy is not taking place, all the energy released by the metabolic processes eventually becomes body heat.

The Calorie. To discuss the metabolic rate of the body and related subjects quantitatively, it is necessary to use some unit for expressing the quantity of energy released from the different foods or expended by the different functional processes of the body. Most often, the *Calorie* is the unit used for this purpose. It will be recalled that 1 *calorie*—spelled with a small "c" and often called a *gram calorie*—is the quantity of heat required to raise the temperature of 1 gram of water 1°C. The calorie is much too small a unit when referring to energy in the body. Consequently, the Calorie—sometimes spelled with a capital "C" and often called a *kilocalorie*, which is equivalent to 1000 calories—is the unit ordinarily used in discussing energy metabolism.

Measurement of the Whole-Body Metabolic Rate

Direct Calorimetry Measures Heat Liberated from the Body. Because a person ordinarily is not performing any external work, the whole-body metabolic rate can be determined by simply measuring the total quantity of heat liberated from the body in a given time.

In determining the metabolic rate by direct calorimetry, one measures the quantity of heat liberated from the body in a large, specially constructed *calorimeter*. The subject is placed in an air chamber that is so well insulated that no heat can leak through the walls of the chamber. Heat formed by the subject's body warms the air of the chamber. However, the air temperature within the chamber is maintained at a constant level by forcing the air through pipes in a cool water bath. The rate of heat gain by the water bath, which can be measured with an accurate thermometer, is equal to the rate at which heat is liberated by the subject's body.

Direct calorimetry is physically difficult to perform and is used only for research purposes.

Indirect Calorimetry—The "Energy Equivalent" of Oxygen. Because more than 95 percent of the energy expended in the body is derived from reactions of oxygen with the different foods, the whole-body metabolic rate can also be calculated with a high degree of accuracy from the rate of oxygen utilization. When 1 liter of oxygen is metabolized with glucose, 5.01 Calories of energy are released; when metabolized with starches, 5.06 Calories are released; with fat, 4.70 Calories; and with protein, 4.60 Calories.

Using these figures, it is striking how nearly equivalent are the quantities of energy liberated per liter of oxygen, regardless of the type of food being metabolized. For the average diet, the *quantity of energy liberated per liter of oxygen used in the body averages about 4.825 Calories*. This is called the *energy equivalent* of oxygen; using this energy equivalent, one can calculate with a high degree of precision the rate of heat liberation in the body from the quantity of oxygen used in a given period of time.

If a person metabolizes only carbohydrates during the period of the metabolic rate determination, the calculated quantity of energy liberated, based on the value for the average energy equivalent of oxygen (4.825 Calories/L), would be about 4 percent too little. Conversely, if the person obtains most energy from fat, the calculated value would be about 4 percent too great.

Energy Metabolism—Factors That Influence Energy Output

As discussed in Chapter 71, energy intake is balanced with energy output in healthy adults who maintain a stable body weight. About 45 percent of daily energy intake is derived from carbohydrates, 40 percent from fats, and 15 percent from proteins in the average American diet. Energy output can also be partitioned into several measurable components, including energy used for (1) performing essential metabolic functions of the body (the "basal" metabolic rate); (2) performing various physical activities; (3) digesting, absorbing, and processing food; and (4) maintaining body temperature.

Overall Energy Requirements for Daily Activities

An average man who weighs 70 kilograms and lies in bed all day uses about 1650 Calories of energy. The process of eating and digesting food increases the amount of energy used each day by an additional 200 or more Calories, so the same man lying in bed and eating a reasonable diet requires a dietary intake of about 1850 Calories per day. If he sits in a chair all day without exercising, his total energy requirement reaches 2000 to 2250 Calories. Therefore, the daily energy requirement for a very sedentary man performing only essential functions is about 2000 Calories.

The amount of energy used to perform daily physical activities is normally about 25 percent of the total energy expenditure, but it can vary markedly in different individuals, depending on the type and amount of physical activity. For example, walking up stairs requires about 17 times as much energy as lying in bed asleep. In general, over a 24-hour period, a person performing heavy labor can achieve a maximal rate of energy utilization as great as 6000 to 7000 Calories, or as much as 3.5 times the energy used under conditions of no physical activity.

Basal Metabolic Rate (BMR)—The Minimum Energy Expenditure for the Body to Exist

Even when a person is at complete rest, considerable energy is required to perform all the chemical reactions of the body. This minimum level of energy required to exist is called the *basal metabolic rate* (BMR) and accounts for about 50 to 70 percent of the daily energy expenditure in most sedentary individuals (Figure 72-3).

Because the level of physical activity is highly variable among different individuals, measurement of the BMR provides a useful means of comparing one person's metabolic rate with that of another. The usual method for determining BMR is to measure the rate of oxygen utilization over a given period of time under the following conditions:

1. The person must not have eaten food for at least 12 hours.
2. The BMR is determined after a night of restful sleep.
3. No strenuous activity is performed for at least 1 hour before the test.
4. All psychic and physical factors that cause excitement must be eliminated.
5. The temperature of the air must be comfortable and between 68° and 80°F.
6. No physical activity is permitted during the test.

The BMR normally averages about 65 to 70 Calories per hour in an average 70-kilogram man. Although much of the BMR is accounted for by essential activities of the central nervous system, heart, kidneys, and other organs, the *variations* in BMR among different individuals are related mainly to differences in the amount of skeletal muscle and body size.

Skeletal muscle, even under resting conditions, accounts for 20 to 30 percent of the BMR. For this reason, BMR is usually corrected for differences in body size by expressing it as Calories per hour per square meter of body surface area, calculated from height and weight. The average values for males and females of different ages are shown in Figure 72-4.

Much of the decline in BMR with increasing age is probably related to loss of muscle mass and replacement of muscle with adipose tissue, which has a lower rate of metabolism. Likewise, slightly lower BMRs in women, compared with men, are due partly to their lower percentage of muscle mass

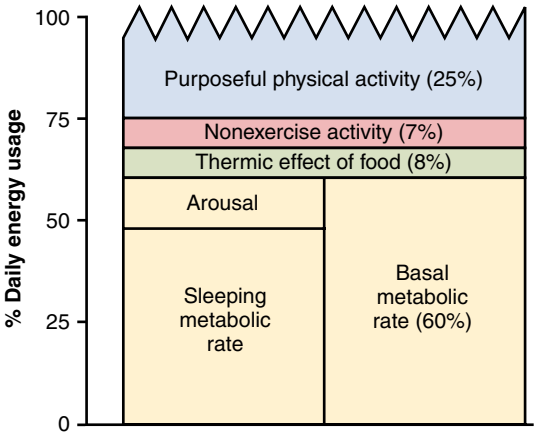


Figure 72-3 Components of energy expenditure.

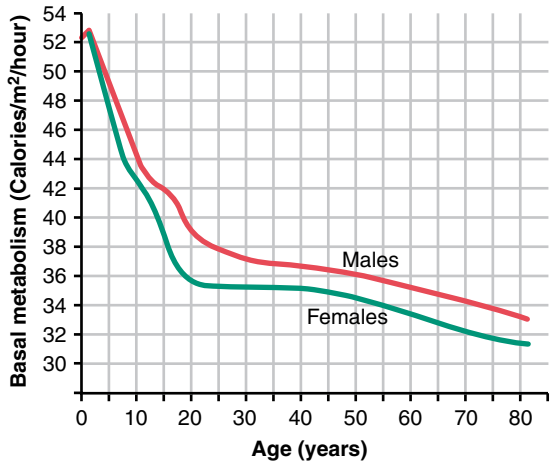


Figure 72-4 Normal basal metabolic rates at different ages for each sex.

and higher percentage of adipose tissue. However, other factors can influence the BMR, as discussed next.

Thyroid Hormone Increases Metabolic Rate. When the thyroid gland secretes maximal amounts of thyroxine, the metabolic rate sometimes rises 50 to 100 percent above normal. Conversely, total loss of thyroid secretion decreases the metabolic rate to 40 to 60 percent of normal. As discussed in Chapter 76, thyroxine increases the rates of the chemical reactions of many cells in the body and therefore increases metabolic rate. Adaptation of the thyroid gland—with increased secretion in cold climates and decreased secretion in hot climates—contributes to the differences in BMRs among people living in different geographical zones; for example, people living in arctic regions have BMRs 10 to 20 percent higher than those of persons living in tropical regions.

Male Sex Hormone Increases Metabolic Rate. The male sex hormone testosterone can increase the metabolic rate about 10 to 15 percent. The female sex hormones may increase the BMR a small amount, but usually not enough to be significant. Much of this effect of the male sex hormone is related to its anabolic effect to increase skeletal muscle mass.

Growth Hormone Increases Metabolic Rate. Growth hormone can increase the metabolic rate by stimulating cellular metabolism and by increasing skeletal muscle mass. In adults with growth hormone deficiency, replacement therapy with recombinant growth hormone increases basal metabolic rate by about 20 percent.

Fever Increases Metabolic Rate. Fever, regardless of its cause, increases the chemical reactions of the body by an average of about 120 percent for every 10 °C rise in temperature. This is discussed in more detail in Chapter 73.

Sleep Decreases Metabolic Rate. The metabolic rate decreases 10 to 15 percent below normal during sleep. This fall is due to two principal factors: (1) decreased tone of the skeletal musculature during sleep and (2) decreased activity of the central nervous system.

Malnutrition Decreases Metabolic Rate. Prolonged malnutrition can decrease the metabolic rate 20 to 30 percent, presumably due to the paucity of food substances in the cells. In the final stages of many disease conditions, the inanition that accompanies the disease causes a marked decrease in metabolic rate, to the extent that the body temperature may fall several degrees shortly before death.

Energy Used for Physical Activities

The factor that most dramatically increases metabolic rate is strenuous exercise. Short bursts of maximal muscle contraction in a single muscle can liberate as much as 100 times its normal resting amount of heat for a few seconds. For the entire body, maximal muscle exercise can increase the overall heat production of the body for a few seconds to about 50 times normal, or to about 20 times normal for more sustained exercise in a well-trained individual.

Table 72-1 shows the energy expenditure during different types of physical activity for a 70-kilogram man. Because of the great variation in the amount of physical activity among individuals, this component of energy expenditure is the most important reason for the differences in caloric intake required to maintain energy balance. However, in industrialized countries where food supplies are plentiful, such as the United States, caloric intake often periodically exceeds energy expenditure, and the excess energy is stored mainly as fat. This underscores the importance of maintaining a proper level of physical activity to prevent excess fat stores and obesity.

Even in sedentary individuals who perform little or no daily exercise or physical work, significant energy is spent on spontaneous physical activity required to maintain muscle tone and body posture and on other nonexercise activities such as "fidgeting." Together, these nonexercise activities account for about 7 percent of a person's daily energy usage.

Energy Used for Processing Food—Thermogenic Effect of Food

After a meal is ingested, the metabolic rate increases as a result of the different chemical reactions associated with digestion, absorption, and storage of food in the body. This is called the *thermogenic effect of food* because these processes require energy and generate heat.

After a meal that contains a large quantity of carbohydrates or fats, the metabolic rate usually increases about 4 percent.

Table 72-1 Energy Expenditure During Different Types of Activity for a 70-Kilogram Man

Form of Activity	Calories per Hour
Sleeping	65
Awake lying still	77
Sitting at rest	100
Standing relaxed	105
Dressing and undressing	118
Typewriting rapidly	140
Walking slowly (2.6 miles per hour)	200
Carpentry, metalworking, industrial painting	240
Sawing wood	480
Swimming	500
Running (5.3 miles per hour)	570
Walking up stairs rapidly	1100

Extracted from data compiled by Professor M.S. Rose.

However, after a high-protein meal, the metabolic rate usually begins rising within an hour, reaching a maximum of about 30 percent above normal, and this lasts for 3 to 12 hours. This effect of protein on the metabolic rate is called the *specific dynamic action of protein*. The thermogenic effect of food accounts for about 8 percent of the total daily energy expenditure in many persons.

Energy Used for Nonshivering Thermogenesis—Role of Sympathetic Stimulation

Although physical work and the thermogenic effect of food cause liberation of heat, these mechanisms are not aimed primarily at regulation of body temperature. Shivering provides a regulated means of producing heat by increasing muscle activity in response to cold stress, as discussed in Chapter 73. Another mechanism, *nonshivering thermogenesis*, can also produce heat in response to cold stress. This type of thermogenesis is stimulated by sympathetic nervous system activation, which releases norepinephrine and epinephrine, which in turn increase metabolic activity and heat generation.

In certain types of fat tissue, called *brown fat*, sympathetic nervous stimulation causes liberation of large amounts of heat. This type of fat contains large numbers of mitochondria and many small globules of fat instead of one large fat globule. In these cells, the process of oxidative phosphorylation in the mitochondria is mainly "uncoupled." That is, when the cells are stimulated by the sympathetic nerves, the mitochondria produce a large amount of heat but almost no ATP, so almost all the released oxidative energy immediately becomes heat.

A neonate has a considerable number of brown fat cells, and maximal sympathetic stimulation can increase the child's metabolism more than 100 percent. The magnitude of this type of thermogenesis in an adult human, who has virtually no brown fat, is probably less than 15 percent, although this might increase significantly after cold adaptation.

Nonshivering thermogenesis may also serve as a buffer against obesity. Recent studies indicate that sympathetic nervous system activity is increased in obese persons who have a persistent excess caloric intake. The mechanism responsible for sympathetic activation in obese persons is uncertain, but it may be mediated partly through the effects of increased leptin, which activates pro-opiomelanocortin neurons in the hypothalamus. Sympathetic stimulation, by increasing thermogenesis, helps to limit excess weight gain.

Bibliography

Argyropoulos G, Harper ME: Uncoupling proteins and thermoregulation, *J Appl Physiol* 92:2187, 2002.

Cahill GF Jr: Fuel metabolism in starvation, *Annu Rev Nutr* 26:1, 2006.

Cannon B, Nedergaard J: Brown adipose tissue: function and physiological significance, *Physiol Rev* 84:277, 2004.

Harper ME, Green K, Brand MD: The efficiency of cellular energy transduction and its implications for obesity, *Annu Rev Nutr* 28:13, 2008.

Harper ME, Seifert EL: Thyroid hormone effects on mitochondrial energetics, *Thyroid* 18:145, 2008.

Kim B: Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate, *Thyroid* 18:141, 2008.

Levine JA: Measurement of energy expenditure, *Public Health Nutr* 8:1123, 2005.

Levine JA, Vander Weg MW, Hill JO, Klesges RC: Non-exercise activity thermogenesis: the crouching tiger, hidden dragon of societal weight gain, *Arterioscler Thromb Vasc Biol* 26:729, 2006.

Lowell BB, Bachman ES: Beta-adrenergic receptors, diet-induced thermogenesis, and obesity, *J Biol Chem* 278:29385, 2003.

Morrison SF, Nakamura K, Madden CJ: Central control of thermogenesis in mammals, *Exp Physiol* 93:773, 2008.

Murphy E, Steenbergen C: Mechanisms underlying acute protection from cardiac ischemia-reperfusion injury, *Physiol Rev* 88:581, 2008.

National Institutes of Health: *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report*, Bethesda, MD, 1998, National Heart, Lung, and Blood Institute and National Institute of Diabetes and Digestive and Kidney Diseases. Available at: http://www.nhlbi.nih.gov/guidelines/index.htm.

Saks V, Favier R, Guzun R, Schlattner U, Wallimann T: Molecular system bioenergetics: regulation of substrate supply in response to heart energy demands, *J Physiol* 15:577, 769, 2006.

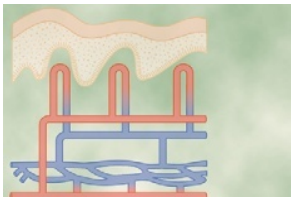
Silva JE: Thermogenic mechanisms and their hormonal regulation, *Physiol Rev* 86:435, 2006.

van Baak MA: Meal-induced activation of the sympathetic nervous system and its cardiovascular and thermogenic effects in man, *Physiol Behav* 94:178, 2008.

Westerterp KR: Limits to sustainable human metabolic rate, *J Exp Biol* 204:3183, 2001.

Westerterp KR: Impacts of vigorous and non-vigorous activity on daily energy expenditure, *Proc Nutr Soc* 62:645, 2003.

Body Temperature Regulation, and Fever



Normal Body Temperatures

Body Core Temperature and Skin Temperature. The temperature of the deep tissues of the body—the "core" of the body—remains very constant, within ±1°F (±0.6°C), except when a person develops a febrile illness. Indeed, a nude person can be exposed to temperatures as low as 55°F or as high as 130°F in *dry* air and still maintain an almost constant core temperature. The mechanisms for regulating body temperature represent a beautifully designed control system. In this chapter we discuss this system as it operates in health and in disease.

The *skin temperature*, in contrast to the *core temperature*, rises and falls with the temperature of the surroundings. The skin temperature is important when we refer to the skin's ability to lose heat to the surroundings.

Normal Core Temperature. No single core temperature can be considered normal because measurements in many healthy people have shown a *range* of normal temperatures measured orally, as shown in Figure 73-1, from less than 97°F (36°C) to over 99.5°F (37.5°C). The average normal core temperature is generally considered to be between 98.0° and 98.6°F when measured orally and about 1°F higher when measured rectally.

The body temperature increases during exercise and varies with temperature extremes of the surroundings because the temperature regulatory mechanisms are not perfect. When excessive heat is produced in the body by strenuous exercise, the temperature can rise temporarily to as high as 101°F to 104°F. Conversely, when the body is exposed to extreme cold, the temperature can fall below 96°F.

Body Temperature Is Controlled by Balancing Heat Production and Heat Loss

When the rate of heat production in the body is greater than the rate at which heat is being lost, heat builds up in the body and the body temperature rises. Conversely, when heat loss is greater, both body heat and body temperature decrease. Most of the remainder of this chapter is concerned with this balance between heat production and heat loss and the mechanisms by which the body controls each of these.

Heat Production

Heat production is a principal by-product of metabolism. In Chapter 72, which summarizes body energetics, we discuss the different factors that determine the rate of heat production, called the *metabolic rate of the body*. The most important of these factors are listed again here: (1) basal rate of metabolism of all the cells of the body; (2) extra rate of metabolism caused by muscle activity, including muscle contractions caused by shivering; (3) extra metabolism caused by the effect of thyroxine (and, to a less extent, other hormones, such as growth hormone and testosterone) on the cells; (4) extra metabolism caused by the effect of epinephrine, norepinephrine, and sympathetic stimulation on the cells; (5) extra metabolism caused by increased chemical activity in the cells themselves, especially when the cell temperature increases; and (6) extra metabolism needed for digestion, absorption, and storage of food (thermogenic effect of food).

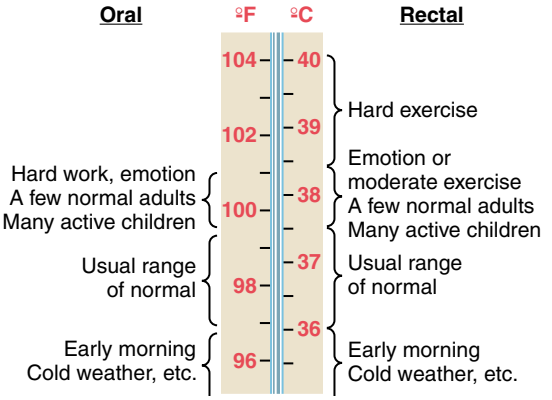


Figure 73-1 Estimated range of body "core" temperature in normal people. (Redrawn from DuBois EF: Fever. Springfield, Ill: Charles C Thomas, 1948.)

Heat Loss

Most of the heat produced in the body is generated in the deep organs, especially in the liver, brain, and heart, and in the skeletal muscles during exercise. Then this heat is transferred from the deeper organs and tissues to the skin, where it is lost to the air and other surroundings. Therefore, the rate at which heat is lost is determined almost entirely by two factors: (1) how rapidly heat can be conducted from where it is produced in the body core to the skin and (2) how rapidly heat can then be transferred from the skin to the surroundings. Let us begin by discussing the system that insulates the core from the skin surface.

Insulator System of the Body

The skin, the subcutaneous tissues, and especially the fat of the subcutaneous tissues act together as a heat insulator for the body. The fat is important because it conducts heat only *one third* as readily as other tissues. When no blood is flowing from the heated internal organs to the skin, the insulating properties of the normal male body are about equal to three-quarters the insulating properties of a usual suit of clothes. In women, this insulation is even better.

The insulation beneath the skin is an effective means of maintaining normal internal core temperature, even though it allows the temperature of the skin to approach the temperature of the surroundings.

Blood Flow to the Skin from the Body Core Provides Heat Transfer

Blood vessels are distributed profusely beneath the skin. Especially important is a continuous venous plexus that is supplied by inflow of blood from the skin capillaries, shown in Figure 73-2. In the most exposed areas of the body—the hands, feet, and ears—blood is also supplied to the plexus directly from the small arteries through highly muscular *arteriovenous anastomoses*.

The rate of blood flow into the skin venous plexus can vary tremendously—from barely above zero to as great as 30 percent of the total cardiac output. A high rate of skin flow causes heat to be conducted from the core of the body to the skin with great efficiency, whereas reduction in the rate of skin flow can decrease the heat conduction from the core to very little.

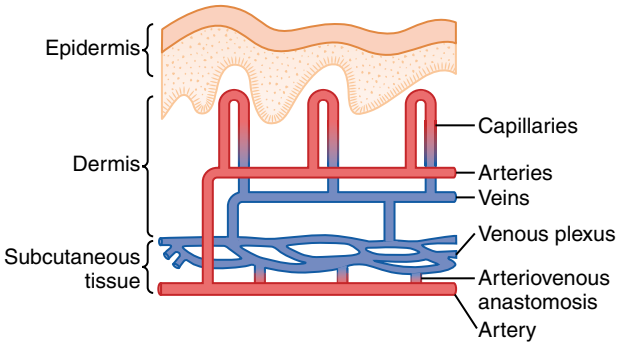


Figure 73-2 Skin circulation.

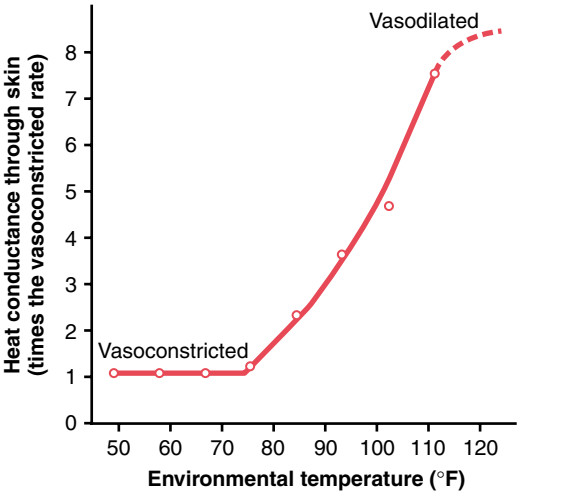


Figure 73-3 Effect of changes in the environmental temperature on heat conductance from the body core to the skin surface. (Modified from Benzinger TH: Heat and Temperature Fundamentals of Medical Physiology. New York: Dowden, Hutchinson & Ross, 1980.)

Figure 73-3 shows quantitatively the effect of environmental air temperature on conductance of heat from the core to the skin surface and then conductance into the air, demonstrating an approximate eightfold increase in heat conductance between the fully vasoconstricted state and the fully vasodilated state.

Therefore, the skin is an effective *controlled "heat radiator" system*, and the flow of blood to the skin is a most effective mechanism for heat transfer from the body core to the skin.

Control of Heat Conduction to the Skin by the Sympathetic Nervous System. Heat conduction to the skin by the blood is controlled by the degree of vasoconstriction of the arterioles and the arteriovenous anastomoses that supply blood to the venous plexus of the skin. This vasoconstriction is controlled almost entirely by the sympathetic nervous system in response to changes in body core temperature and changes in environmental temperature. This is discussed later in the chapter in connection with control of body temperature by the hypothalamus.

Basic Physics of How Heat Is Lost from the Skin Surface

The various methods by which heat is lost from the skin to the surroundings are shown in Figure 73-4. They include *radiation, conduction*, and *evaporation*, which are explained next.

Radiation. As shown in Figure 73-4, in a nude person sitting inside at normal room temperature, about 60 percent of total heat loss is by radiation.

Loss of heat by radiation means loss in the form of infrared heat rays, a type of electromagnetic wave. Most infrared heat rays that radiate from the body have wavelengths of 5 to 20 micrometers, 10 to 30 times the wavelengths of light rays. All objects that are not at absolute zero temperature radiate such rays. The human body

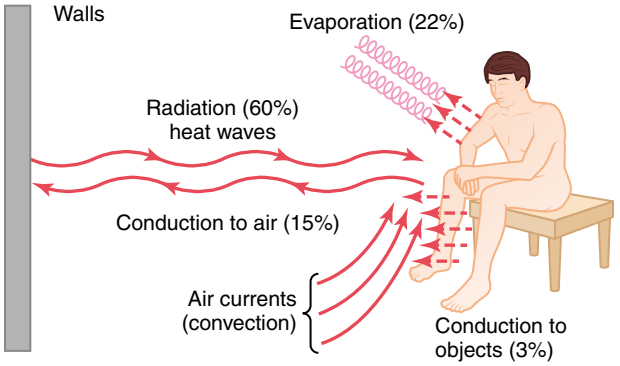


Figure 73-4 Mechanisms of heat loss from the body.

radiates heat rays in all directions. Heat rays are also being radiated from the walls of rooms and other objects toward the body. If the temperature of the body is greater than the temperature of the surroundings, a greater quantity of heat is radiated from the body than is radiated to the body.

Conduction. As shown in Figure 73-4, only minute quantities of heat, about 3 percent, are normally lost from the body by direct conduction from the surface of the body to *solid objects*, such as a chair or a bed. Loss of heat by *conduction to air*, however, represents a sizable proportion of the body's heat loss (about 15 percent) even under normal conditions.

It will be recalled that heat is actually the kinetic energy of molecular motion, and the molecules of the skin are continually undergoing vibratory motion. Much of the energy of this motion can be transferred to the air if the air is colder than the skin, thus increasing the velocity of the air molecules' motion. Once the temperature of the air adjacent to the skin equals the temperature of the skin, no further loss of heat occurs in this way because now an equal amount of heat is conducted from the air to the body. Therefore, conduction of heat from the body to the air is self-limited *unless the heated air moves away from the skin*, so new, unheated air is continually brought in contact with the skin, a phenomenon called *air convection*.

Convection. The removal of heat from the body by convection air currents is commonly called *heat loss by convection*. Actually, the heat must first be *conducted* to the air and then carried away by the convection air currents.

A small amount of convection almost always occurs around the body because of the tendency for air adjacent to the skin to rise as it becomes heated. Therefore, in a nude person seated in a comfortable room without gross air movement, about 15 percent of his or her total heat loss occurs by conduction to the air and then by air convection away from the body.

Cooling Effect of Wind. When the body is exposed to wind, the layer of air immediately adjacent to the skin is replaced by new air much more rapidly than normally, and heat loss by convection increases accordingly. The cooling effect of wind at low velocities is about proportional to the *square root of the wind velocity*. For instance, a wind of 4 miles per hour is about twice as effective for cooling as a wind of 1 mile per hour.

Conduction and Convection of Heat from a Person Suspended in Water. Water has a specific heat several thousand times as great as that of air, so each unit portion of water adjacent to the skin can absorb far greater quantities of heat than air can. Also, heat conductivity in water is very great in comparison with that in air. Consequently, it is impossible for the body to heat a thin layer of water next to the body to form an "insulator zone" as occurs in air. Therefore, the rate of heat loss to water is usually many times greater than the rate of heat loss to air.

Evaporation. When water evaporates from the body surface, 0.58 Calorie (kilocalorie) of heat is lost for each gram of water that evaporates. Even when a person is not sweating, water still evaporates *insensibly* from the skin and lungs at a rate of about 600 to 700 ml/day. This causes continual heat loss at a rate of 16 to 19 Calories per hour. This insensible evaporation through the skin and lungs cannot be controlled for purposes of temperature regulation because it results from continual diffusion of water molecules through the skin and respiratory surfaces. However, loss of heat by *evaporation of sweat* can be controlled by regulating the rate of sweating, which is discussed later in the chapter.

Evaporation Is a Necessary Cooling Mechanism at Very High Air Temperatures. As long as skin temperature is greater than the temperature of the surroundings, heat can be lost by radiation and conduction. But when the temperature of the surroundings becomes greater than that of the skin, instead of losing heat, the body gains heat by both radiation and conduction. Under these conditions, *the only means by which the body can rid itself of heat is by evaporation*.

Therefore, anything that prevents adequate evaporation when the surrounding temperature is higher than the skin temperature will cause the internal body temperature to rise. This occurs occasionally in human beings who are born with congenital absence of sweat glands. These people can tolerate cold temperatures as well as normal people can, but they are likely to die of heatstroke in tropical zones because without the evaporative refrigeration system, they cannot prevent a rise in body temperature when the air temperature is above that of the body.

Effect of Clothing on Conductive Heat Loss. Clothing entraps air next to the skin in the weave of the cloth, thereby increasing the thickness of the so-called *private zone* of air adjacent to the skin and also decreasing the flow of convection air currents. Consequently, the rate of heat loss from the body by conduction and convection is greatly depressed. A usual suit of clothes decreases the rate of heat loss to about half that from the nude body, but arctic-type clothing can decrease this heat loss to as little as one sixth.

About half the heat transmitted from the skin to the clothing is radiated to the clothing instead of being conducted across the small intervening space. Therefore, coating the inside of clothing with a thin layer of gold,

which reflects radiant heat back to the body, makes the insulating properties of clothing far more effective than otherwise. Using this technique, clothing for use in the arctic can be decreased in weight by about half.

The effectiveness of clothing in maintaining body temperature is almost completely lost when the clothing becomes wet because the high conductivity of water increases the rate of heat transmission through cloth 20-fold or more. Therefore, one of the most important factors for protecting the body against cold in arctic regions is extreme caution against allowing the clothing to become wet. Indeed, one must be careful not to become overheated even temporarily because sweating in one's clothes makes them much less effective thereafter as an insulator.

Sweating and Its Regulation by the Autonomic Nervous System

Stimulation of the anterior hypothalamus-preoptic area in the brain either electrically or by excess heat causes sweating. The nerve impulses from this area that cause sweating are transmitted in the autonomic pathways to the spinal cord and then through sympathetic outflow to the skin everywhere in the body.

It should be recalled from the discussion of the autonomic nervous system in Chapter 60 that the sweat glands are innervated by *cholinergic* nerve fibers (fibers that secrete acetylcholine but that run in the sympathetic nerves along with the adrenergic fibers). These glands can also be stimulated to some extent by epinephrine or norepinephrine circulating in the blood, even though the glands themselves do not have adrenergic innervation. This is important during exercise, when these hormones are secreted by the adrenal medullae and the body needs to lose excessive amounts of heat produced by the active muscles.

Mechanism of Sweat Secretion. In Figure 73-5, the sweat gland is shown to be a tubular structure consisting of two parts: (1) a deep subdermal *coiled portion* that secretes the sweat, and (2) a *duct portion* that passes outward through the dermis and epidermis of the skin. As is true of so many other glands, the secretory portion of the sweat gland secretes a fluid called the *primary secretion* or *precursor secretion*; the concentrations of constituents in the fluid are then modified as the fluid flows through the duct.

The precursor secretion is an active secretory product of the epithelial cells lining the coiled portion of the sweat gland. Cholinergic sympathetic nerve fibers ending on or near the glandular cells elicit the secretion.

The composition of the precursor secretion is similar to that of plasma, except that it does not contain plasma proteins. The concentration of sodium is about 142 mEq/L and that of chloride is about 104 mEq/L, with much smaller concentrations of the other solutes of plasma. As this precursor solution flows through the duct portion of the gland, it is modified by reabsorption of most of the sodium and chloride ions. The degree of this reabsorption depends on the rate of sweating, as follows.

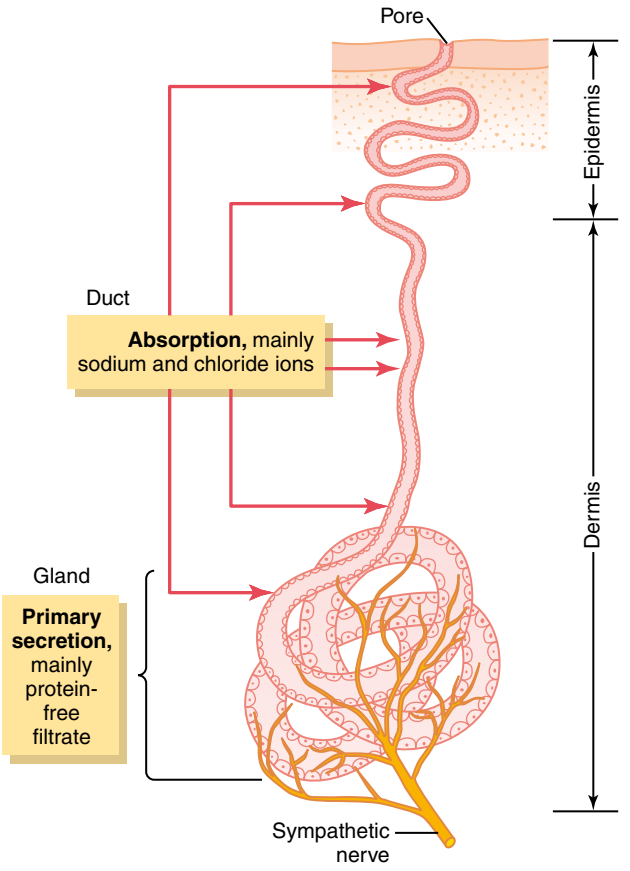


Figure 73-5 Sweat gland innervated by an acetylcholine-secreting sympathetic nerve. A *primary protein-free secretion* is formed by the glandular portion, but most of the electrolytes are reabsorbed in the duct, leaving a dilute, watery secretion.

When the sweat glands are stimulated only slightly, the precursor fluid passes through the duct slowly. In this instance, essentially all the sodium and chloride ions are reabsorbed, and the concentration of each falls to as low as 5 mEq/L. This reduces the osmotic pressure of the sweat fluid to such a low level that most of the water is also reabsorbed, which concentrates most of the other constituents. Therefore, at low rates of sweating, such constituents as urea, lactic acid, and potassium ions are usually very concentrated.

Conversely, when the sweat glands are strongly stimulated by the sympathetic nervous system, large amounts of precursor secretion are formed, and the duct may reabsorb only slightly more than half the sodium chloride; the concentrations of sodium and chloride ions are then (in an *unacclimatized* person) a maximum of about 50 to 60 mEq/L, slightly less than half the concentrations in plasma. Furthermore, the sweat flows through the glandular tubules so rapidly that little of the water is reabsorbed. Therefore, the other dissolved constituents of sweat are only moderately increased in concentration—urea is about twice that in the plasma, lactic acid about 4 times, and potassium about 1.2 times.

There is a significant loss of sodium chloride in the sweat when a person is unacclimatized to heat. There is much

less electrolyte loss, despite increased sweating capacity, once a person has become acclimatized, as follows.

Acclimatization of the Sweating Mechanism to Heat—Role of Aldosterone. Although a normal, unacclimatized person seldom produces more than about 1 liter of sweat per hour, when this person is exposed to hot weather for 1 to 6 weeks, he or she begins to sweat more profusely, often increasing maximum sweat production to as much as 2 to 3 L/hour. Evaporation of this much sweat can remove heat from the body at a rate *more than 10 times* the normal basal rate of heat production. This increased effectiveness of the sweating mechanism is caused by a change in the internal sweat gland cells themselves to increase their sweating capability.

Also associated with acclimatization is a further decrease in the concentration of sodium chloride in the sweat, which allows progressively better conservation of body salt. Most of this effect is caused by *increased secretion of aldosterone* by the adrenocortical glands, which results from a slight decrease in sodium chloride concentration in the extracellular fluid and plasma. An *unacclimatized* person who sweats profusely often loses 15 to 30 grams of salt each day for the first few days. After 4 to 6 weeks of acclimatization, the loss is usually 3 to 5 g/day.

Loss of Heat by Panting

Many lower animals have little ability to lose heat from the surfaces of their bodies, for two reasons: (1) the surfaces are often covered with fur, and (2) the skin of most lower animals is not supplied with sweat glands, which prevents most of the evaporative loss of heat from the skin. A substitute mechanism, the *panting* mechanism, is used by many lower animals as a means of dissipating heat.

The phenomenon of panting is "turned on" by the thermoregulator centers of the brain. That is, when the blood becomes overheated, the hypothalamus initiates neurogenic signals to decrease the body temperature. One of these signals initiates panting. The actual panting process is controlled by a *panting center* that is associated with the pneumotaxic respiratory center located in the pons.

When an animal pants, it breathes in and out rapidly, so large quantities of new air from the exterior come in contact with the upper portions of the respiratory passages; this cools the blood in the respiratory passage mucosa as a result of water evaporation from the mucosal surfaces, especially evaporation of saliva from the tongue. Yet panting does not increase the alveolar ventilation more than is required for proper control of the blood gases because each breath is extremely shallow; therefore, most of the air that enters the alveoli is dead-space air mainly from the trachea and not from the atmosphere.

Regulation of Body Temperature—Role of the Hypothalamus

Figure 73-6 shows what happens to the body "core" temperature of a nude person after a few hours' exposure to *dry* air ranging from 30° to 160°F. The precise dimensions of this curve depend on the wind movement of the air, the amount of moisture in the air, and even the nature of the surroundings. In general, a nude person in dry air between 55° and 130° F is capable of maintaining a normal body core temperature somewhere between 97° and 100°F.

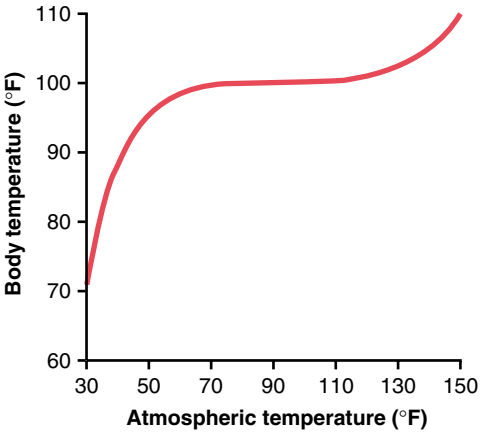


Figure 73-6 Effect of high and low atmospheric temperatures of several hours' duration, under dry conditions, on the internal body "core" temperature. Note that the internal body temperature remains stable despite wide changes in atmospheric temperature.

The temperature of the body is regulated almost entirely by nervous feedback mechanisms, and almost all these operate through *temperature-regulating centers* located in the *hypothalamus*. For these feedback mechanisms to operate, there must also be temperature detectors to determine when the body temperature becomes either too high or too low.

Role of the Anterior Hypothalamic-Preoptic Area in Thermostatic Detection of Temperature

Experiments have been performed in which minute areas in the brain of an animal have been either heated or cooled by use of a *thermode*. This small, needle-like device is heated by electrical means or by passing hot water through it, or it is cooled by cold water. The principal areas in the brain where heat or cold from a thermode affects body temperature control are the preoptic and anterior hypothalamic nuclei of the hypothalamus.

Using the thermode, the anterior hypothalamic-preoptic area has been found to contain large numbers of heat-sensitive neurons, as well as about one-third as many cold-sensitive neurons. These neurons are believed to function as temperature sensors for controlling body temperature. The heat-sensitive neurons increase their firing rate 2- to 10-fold in response to a 10°C increase in body temperature. The cold-sensitive neurons, by contrast, increase their firing rate when the body temperature falls.

When the preoptic area is heated, the skin all over the body immediately breaks out in a profuse sweat, whereas the skin blood vessels over the entire body become greatly dilated. This is an immediate reaction to cause the body to lose heat, thereby helping to return the body temperature toward the normal level. In addition, any excess body heat production is inhibited. Therefore, it is clear that the hypothalamic-preoptic area has the capability to serve as a thermostatic body temperature control center.

Detection of Temperature by Receptors in the Skin and Deep Body Tissues

Although the signals generated by the temperature receptors of the hypothalamus are extremely powerful in controlling body temperature, receptors in other parts of the body play additional roles in temperature regulation. This is especially true of temperature receptors in the skin and in a few specific deep tissues of the body.

It will be recalled from the discussion of sensory receptors in Chapter 48 that the skin is endowed with both *cold* and *warmth* receptors. There are far more cold receptors than warmth receptors—in fact, 10 times as many in many parts of the skin. Therefore, peripheral detection of temperature mainly concerns detecting cool and cold instead of warm temperatures.

When the skin is chilled over the entire body, immediate reflex effects are invoked and begin to increase the temperature of the body in several ways: (1) by providing a strong stimulus to cause shivering, with a resultant increase in the rate of body heat production; (2) by inhibiting the process of sweating, if this is already occurring; and (3) by promoting skin vasoconstriction to diminish loss of body heat from the skin.

Deep body temperature receptors are found mainly in the *spinal cord*, in the *abdominal viscera*, and in or around the *great veins* in the upper abdomen and thorax. These deep receptors function differently from the skin receptors because they are exposed to the body core temperature rather than the body surface temperature. Yet, like the skin temperature receptors, they detect mainly cold rather than warmth. It is probable that both the skin and the deep body receptors are concerned with preventing *hypothermia*—that is, preventing low body temperature.

Posterior Hypothalamus Integrates the Central and Peripheral Temperature Sensory Signals

Even though many temperature sensory signals arise in peripheral receptors, these signals contribute to body temperature control mainly through the hypothalamus. The area of the hypothalamus that they stimulate is located bilaterally in the posterior hypothalamus approximately at the level of the mammillary bodies. The temperature sensory signals from the anterior hypothalamic-preoptic area are also transmitted into this posterior hypothalamic area. Here the signals from the preoptic area and the signals from elsewhere in the body are combined and integrated to control the heat-producing and heat-conserving reactions of the body.

Neuronal Effector Mechanisms That Decrease or Increase Body Temperature

When the hypothalamic temperature centers detect that the body temperature is either too high or too low, they institute appropriate temperature-decreasing or temperature-increasing procedures. The reader is probably familiar with most of these from personal experience, but special features are the following.

Temperature-Decreasing Mechanisms When the Body Is Too Hot

The temperature control system uses three important mechanisms to reduce body heat when the body temperature becomes too great:

1. *Vasodilation of skin blood vessels.* In almost all areas of the body, the skin blood vessels become intensely dilated. This is caused by inhibition of the sympathetic centers in the posterior hypothalamus that cause vasoconstriction. Full vasodilation can increase the rate of heat transfer to the skin as much as eightfold.
2. *Sweating.* The effect of increased body temperature to cause sweating is demonstrated by the blue curve in Figure 73-7, which shows a sharp increase in the rate of evaporative heat loss resulting from sweating when the body core temperature rises above the critical level of 37°C (98.6°F). An additional 1°C increase in body temperature causes enough sweating to remove 10 times the basal rate of body heat production.
3. *Decrease in heat production.* The mechanisms that cause excess heat production, such as shivering and chemical thermogenesis, are strongly inhibited.

Temperature-Increasing Mechanisms When the Body Is Too Cold

When the body is too cold, the temperature control system institutes exactly opposite procedures. They are:

1. *Skin vasoconstriction throughout the body.* This is caused by stimulation of the posterior hypothalamic sympathetic centers.
2. *Piloerection.* Piloerection means hairs "standing on end." Sympathetic stimulation causes the arrector pili

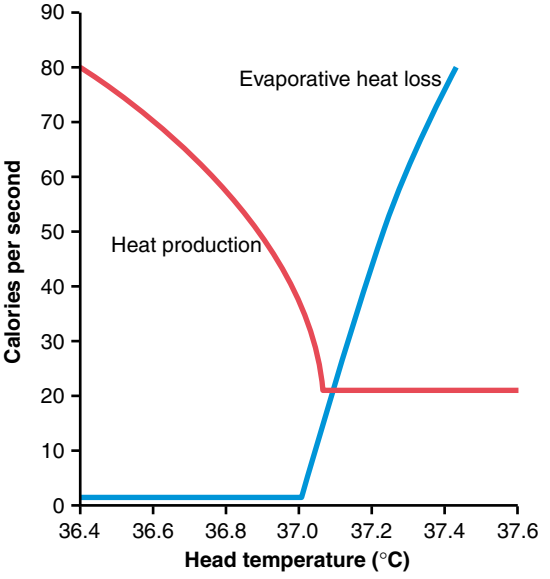


Figure 73-7 Effect of hypothalamic temperature on evaporative heat loss from the body and on heat production caused primarily by muscle activity and shivering. This figure demonstrates the extremely critical temperature level at which increased heat loss begins and heat production reaches a minimum stable level.

muscles attached to the hair follicles to contract, which brings the hairs to an upright stance. This is not important in human beings, but in lower animals, upright projection of the hairs allows them to entrap a thick layer of "insulator air" next to the skin, so transfer of heat to the surroundings is greatly depressed.

3. *Increase in thermogenesis (heat production).* Heat production by the metabolic systems is increased by promoting shivering, sympathetic excitation of heat production, and thyroxine secretion. These methods of increasing heat require additional explanation, which follows.

Hypothalamic Stimulation of Shivering. Located in the dorsomedial portion of the posterior hypothalamus near the wall of the third ventricle is an area called the *primary motor center for shivering*. This area is normally inhibited by signals from the heat center in the anterior hypothalamic-preoptic area but is excited by cold signals from the skin and spinal cord. Therefore, as shown by the sudden increase in "heat production" (see the red curve in Figure 73-7), this center becomes activated when the body temperature falls even a fraction of a degree below a critical temperature level. It then transmits signals that cause shivering through bilateral tracts down the brain stem, into the lateral columns of the spinal cord, and finally to the anterior motor neurons. These signals are nonrhythmical and do not cause the actual muscle shaking. Instead, they increase the tone of the skeletal muscles throughout the body by facilitating the activity of the anterior motor neurons. When the tone rises above a certain critical level, shivering begins. This probably results from feedback oscillation of the muscle spindle stretch reflex mechanism, which is discussed in Chapter 54. *During maximum shivering, body heat production can rise to four to five times normal.*

Sympathetic "Chemical" Excitation of Heat Production. As pointed out in Chapter 72, an increase in either sympathetic stimulation or circulating norepinephrine and epinephrine in the blood can cause an immediate increase in the rate of cellular metabolism. This effect is called *chemical thermogenesis*, or *nonshivering thermogenesis*. It results at least partially from the ability of norepinephrine and epinephrine to *uncouple* oxidative phosphorylation, which means that excess foodstuffs are oxidized and thereby release energy in the form of heat but do not cause ATP to be formed.

The degree of chemical thermogenesis that occurs in an animal is almost directly proportional to the amount of *brown fat* in the animal's tissues. This is a type of fat that contains large numbers of special mitochondria where uncoupled oxidation occurs, as described in Chapter 72. Brown fat is richly supplied with sympathetic nerves that release norepinephrine, which stimulates tissue expression of *mitochondrial uncoupling protein* (also called *thermogenin*) and increases thermogenesis.

Acclimatization greatly affects the intensity of chemical thermogenesis; some animals, such as rats, that have been exposed to a cold environment for several weeks exhibit a 100 to 500 percent increase in heat production when acutely exposed to cold, in contrast to the unacclimatized animal, which responds with an increase of perhaps one third as much. This increased thermogenesis also leads to a corresponding increase in food intake.

In adult human beings, who have almost no brown fat, it is rare for chemical thermogenesis to increase the rate of heat production more than 10 to 15 percent. However, in infants, who *do* have a small amount of brown fat in the interscapular space, chemical thermogenesis can increase the rate of heat production 100 percent, which is probably an important factor in maintaining normal body temperature in neonates.

Increased Thyroxine Output as a Long-Term Cause of Increased Heat Production. Cooling the anterior hypothalamic-preoptic area also increases production of the neurosecretory hormone *thyrotropin-releasing hormone* by the hypothalamus. This hormone is carried by way of the hypothalamic portal veins to the anterior pituitary gland, where it stimulates secretion of *thyroid-stimulating hormone*.

Thyroid-stimulating hormone in turn stimulates increased output of *thyroxine* by the thyroid gland, as explained in Chapter 76. The increased thyroxine activates uncoupling protein and increases the rate of cellular metabolism throughout the body, which is yet another mechanism of *chemical thermogenesis*. This increase in metabolism does not occur immediately but requires several weeks' exposure to cold to make the thyroid gland hypertrophy and reach its new level of thyroxine secretion.

Exposure of animals to extreme cold for several weeks can cause their thyroid glands to increase in size 20 to 40 percent. However, human beings seldom allow themselves to be exposed to the same degree of cold as that to which animals are often subjected. Therefore, we still do not know, quantitatively, how important the thyroid mechanism of adaptation to cold is in the human being.

Isolated measurements have shown that military personnel residing for several months in the arctic develop increased metabolic rates; some Inuit (Eskimos) also have abnormally high basal metabolic rates. Further, the continuous stimulatory effect of cold on the thyroid gland may explain the much higher incidence of toxic thyroid goiters in people who live in cold climates than in those who live in warm climates.

Concept of a "Set-Point" for Temperature Control

In the example of Figure 73-7, it is clear that at a critical body core temperature of about 37.1°C (98.8°F), drastic changes occur in the rates of both heat loss and heat production. At temperatures above this level, the rate of heat loss is greater than that of heat production, so the body temperature falls and approaches the 37.1°C level. At temperatures below this level, the rate of heat production is greater than that of heat loss, so the body temperature

rises and again approaches the 37.1°C level. This crucial temperature level is called the "set-point" of the temperature control mechanism. That is, all the temperature control mechanisms continually attempt to bring the body temperature back to this set-point level.

Feedback Gain for Body Temperature Control. Let us recall the discussion of feedback gain of control systems presented in Chapter 1. Feedback gain is a measure of the effectiveness of a control system. In the case of body temperature control, it is important for the internal core temperature to change as little as possible, even though the environmental temperature might change greatly from day to day or even hour to hour. The *feedback gain* of the temperature control system is equal to the ratio of the change in environmental temperature to the change in body core temperature minus 1.0 (see Chapter 1 for this formula). Experiments have shown that the body temperature of humans changes about 1°C for each 25° to 30°C change in environmental temperature. Therefore, the feedback gain of the total mechanism for body temperature control averages about 27 (28/1.0 – 1.0 = 27), which is an extremely high gain for a biological control system (the baroreceptor arterial pressure control system, by comparison, has a feedback gain of <2).

Skin Temperature Can Slightly Alter the Set-Point for Core Temperature Control

The critical temperature set-point in the hypothalamus above which sweating begins and below which shivering begins is determined mainly by the degree of activity of the heat temperature receptors in the anterior hypothalamic-preoptic area. However, temperature signals from the peripheral areas of the body, especially from the skin and certain deep body tissues (spinal cord and abdominal viscera), also contribute slightly to body temperature regulation. But how do they contribute? The answer is that they alter the set-point of the hypothalamic temperature control center. This effect is shown in Figures 73-8 and 73-9.

Figure 73-8 demonstrates the effect of different skin temperatures on the set-point for sweating, showing that the set-point increases as the skin temperature decreases. Thus, for the person represented in this figure, the hypothalamic set-point increased from 36.7°C when the skin temperature was higher than 33°C to a set-point of 37.4°C when the skin temperature had fallen to 29°C. Therefore, when the skin temperature was high, sweating began at a lower hypothalamic temperature than when the skin temperature was low. One can readily understand the value of such a system because it is important that sweating be inhibited when the skin temperature is low; otherwise, the combined effect of low skin temperature and sweating could cause far too much loss of body heat.

A similar effect occurs in shivering, as shown in Figure 73-9. That is, when the skin becomes cold, it drives the

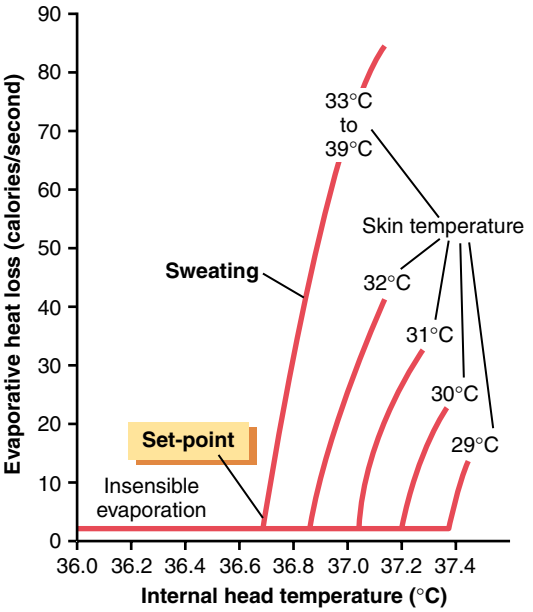


Figure 73-8 Effect of changes in the internal head temperature on the rate of evaporative heat loss from the body. Note that the skin temperature determines the set-point level at which sweating begins. (Courtesy Dr. T. H. Benzinger.)

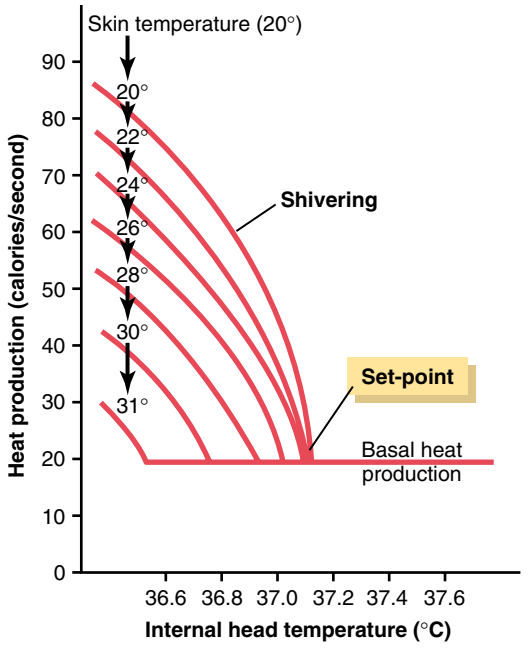


Figure 73-9 Effect of changes in the internal head temperature on the rate of heat production by the body. Note that the skin temperature determines the set-point level at which shivering begins. (Courtesy Dr. T. H. Benzinger.)

hypothalamic centers to the shivering threshold even when the hypothalamic temperature itself is still on the hot side of normal. Here again, one can understand the value of the control system because a cold skin temperature would soon lead to a deeply depressed body temperature unless heat production were increased. Thus, a cold skin temperature actually "anticipates" a fall in internal body temperature and prevents this.

Behavioral Control of Body Temperature

Aside from the subconscious mechanisms for body temperature control, the body has another temperature-control mechanism that is even more potent. This is *behavioral control of temperature*, which can be explained as follows: Whenever the internal body temperature becomes too high, signals from the temperature-controlling areas in the brain give the person a psychic sensation of being overheated. Conversely, whenever the body becomes too cold, signals from the skin and probably also from some deep body receptors elicit the feeling of cold discomfort. Therefore, the person makes appropriate environmental adjustments to re-establish comfort, such as moving into a heated room or wearing well-insulated clothing in freezing weather. This is a much more powerful system of body temperature control than most physiologists have acknowledged in the past. Indeed, this is the only really effective mechanism to maintain body heat control in severely cold environments.

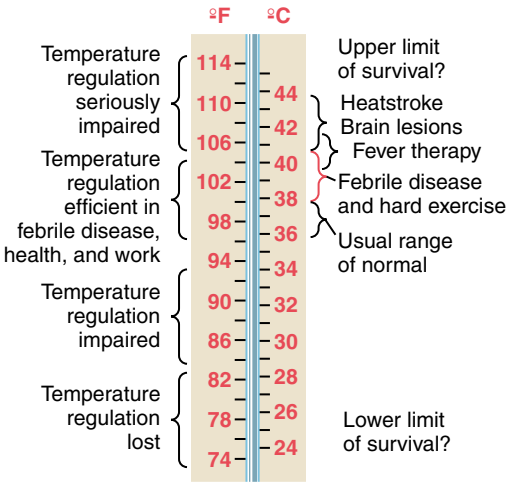


Figure 73-10 Body temperatures under different conditions. (Redrawn from DuBois EF: Fever. Springfield, Ill: Charles C Thomas, 1948.)

Local Skin Temperature Reflexes

When a person places a foot under a hot lamp and leaves it there for a short time, *local vasodilation* and mild *local sweating* occur. Conversely, placing the foot in cold water causes local vasoconstriction and local cessation of sweating. These reactions are caused by local effects of temperature directly on the blood vessels and also by local cord reflexes conducted from skin receptors to the spinal cord and back to the same skin area and the sweat glands. The *intensity* of these local effects is, in addition, controlled by the central brain temperature controller, so their overall effect is proportional to the hypothalamic heat control signal *times* the local signal. Such reflexes can help prevent excessive heat exchange from locally cooled or heated portions of the body.

Regulation of Internal Body Temperature Is Impaired by Cutting the Spinal Cord. After cutting the spinal cord in the neck above the sympathetic outflow from the cord, regulation of body temperature becomes extremely poor because the hypothalamus can no longer control either skin blood flow or the degree of sweating anywhere in the body. This is true even though the local temperature reflexes originating in the skin, spinal cord, and intra-abdominal receptors still exist. These reflexes are extremely weak in comparison with hypothalamic control of body temperature.

In people with this condition, body temperature must be regulated principally by the patient's psychic response to cold and hot sensations in the head region—that is, by behavioral control of clothing and by moving into an appropriate warm or cold environment.

Abnormalities of Body Temperature Regulation

Fever

Fever, which means a body temperature above the usual range of normal, can be caused by abnormalities in the brain itself or by toxic substances that affect the temperature-regulating centers. Some causes of fever (and also of subnormal body temperatures) are presented in Figure 73-10. They include bacterial diseases, brain tumors, and environmental conditions that may terminate in heatstroke.

Resetting the Hypothalamic Temperature-Regulating Center in Febrile Diseases—Effect of Pyrogens

Many proteins, breakdown products of proteins, and certain other substances, especially lipopolysaccharide toxins released from bacterial cell membranes, can cause the set-point of the hypothalamic thermostat to rise. Substances that cause this effect are called *pyrogens*. Pyrogens released from toxic bacteria or those released from degenerating body tissues cause fever during disease conditions. When the set-point of the hypothalamic temperature-regulating center becomes higher than normal, all the mechanisms for raising the body temperature are brought into play, including heat conservation and increased heat production. Within a few hours after the set-point has been increased, the body temperature also approaches this level, as shown in Figure 73-11.

Mechanism of Action of Pyrogens in Causing Fever—Role of Cytokines. Experiments in animals have shown that some pyrogens, when injected into the hypothalamus, can act directly and immediately on the hypothalamic temperature-regulating center to increase its set-point. Other pyrogens function indirectly and may require several hours of latency before causing their effects. This is true of many of the bacterial pyrogens, especially the *endotoxins* from gram-negative bacteria.

When bacteria or breakdown products of bacteria are present in the tissues or in the blood, they are *phagocytized by the blood leukocytes, by tissue macrophages*, and *by large granular killer lymphocytes*. All these cells digest the bacterial products and then release cytokines, a diverse group of peptide signaling molecules involved in the innate and adaptive immune responses. One of the most important of these cytokines in causing fever is *interleukin-1 (IL-1)*, also called *leukocyte pyrogen* or

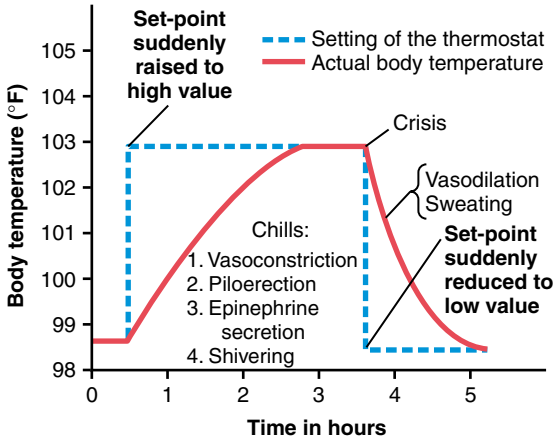


Figure 73-11 Effects of changing the set-point of the hypothalamic temperature controller.

endogenous pyrogen. Interleukin-1 is released from macrophages into the body fluids and, on reaching the hypothalamus, almost immediately activates the processes to produce fever, sometimes increasing the body temperature a noticeable amount in only 8 to 10 minutes. *As little as one ten millionth of a gram of endotoxin lipopolysaccharide* from bacteria, acting in concert with the blood leukocytes, tissue macrophages, and killer lymphocytes, can cause fever. The amount of interleukin-1 that is formed in response to lipopolysaccharide to cause fever is only a few nanograms.

Several experiments have suggested that interleukin-1 causes fever by first inducing the formation of one of the prostaglandins, mainly prostaglandin E_2, or a similar substance, which acts in the hypothalamus to elicit the fever reaction. When prostaglandin formation is blocked by drugs, the fever is either completely abrogated or at least reduced. In fact, this may be the explanation for the manner in which aspirin reduces fever because aspirin impedes the formation of prostaglandins from arachidonic acid. Drugs such as aspirin that reduce fever are called *antipyretics*.

Fever Caused by Brain Lesions. When a brain surgeon operates in the region of the hypothalamus, severe fever almost always occurs; rarely, the opposite effect, hypothermia, occurs, demonstrating both the potency of the hypothalamic mechanisms for body temperature control and the ease with which abnormalities of the hypothalamus can alter the set-point of temperature control. Another condition that frequently causes prolonged high temperature is compression of the hypothalamus by a brain tumor.

Characteristics of Febrile Conditions

Chills. When the set-point of the hypothalamic temperature-control center is suddenly changed from the normal level to higher than normal (as a result of tissue destruction, pyrogenic substances, or dehydration), the body temperature usually takes several hours to reach the new temperature set-point.

Figure 73-11 demonstrates the effect of suddenly increasing the temperature set-point to a level of 103°F. Because the blood temperature is now less than the set-point of the hypothalamic temperature controller, the usual responses that cause elevation of body temperature occur. During this period, the person experiences chills and feels extremely cold, even though his or her body temperature may already be above normal. Also, the skin becomes cold because of vasoconstriction and the person shivers. Chills can continue until the body temperature reaches the hypothalamic set-point of 103°F. Then the person no longer experiences chills but instead feels neither cold nor hot. As long as the factor that is causing the higher set-point of the hypothalamic temperature controller is present, the body temperature is regulated more or less in the normal manner, but at the high temperature set-point level.

Crisis, or "Flush". If the factor that is causing the high temperature is removed, the set-point of the hypothalamic temperature controller will be reduced to a lower value—perhaps even back to the normal level, as shown in Figure 73-11. In this instance, the body temperature is still 103°F, but the hypothalamus is attempting to regulate the temperature to 98.6°F. This situation is analogous to excessive heating of the anterior hypothalamic-preoptic area, which causes intense sweating and the sudden development of hot skin because of vasodilation everywhere. This sudden change of events in a febrile state is known as the "crisis" or, more appropriately, the "flush." In the days before the advent of antibiotics, the crisis was always anxiously awaited because once this occurred, the doctor assumed that the patient's temperature would soon begin falling.

Heatstroke

The upper limit of air temperature that one can stand depends to a great extent on whether the air is dry or wet. If the air is dry and sufficient convection air currents are flowing to promote rapid evaporation from the body, a person can withstand several hours of air temperature at 130°F. Conversely, if the air is 100 percent humidified or if the body is in water, the body temperature begins to rise whenever the environmental temperature rises above about 94°F. If the person is performing heavy work, the critical *environmental temperature* above which heatstroke is likely to occur may be as low as 85° to 90°F.

When the body temperature rises beyond a critical temperature, into the range of 105° to 108°F, the person is likely to develop *heatstroke*. The symptoms include dizziness, abdominal distress sometimes accompanied by vomiting, sometimes delirium, and eventually loss of consciousness if the body temperature is not soon decreased. These symptoms are often exacerbated by a degree of *circulatory shock* brought on by excessive loss of fluid and electrolytes in the sweat.

The hyperpyrexia itself is also exceedingly damaging to the body tissues, especially the brain, and is responsible for many of the effects. In fact, even a few minutes of very high body temperature can sometimes be fatal. For this reason, many authorities recommend immediate treatment of heatstroke by placing the person in a cold water bath. Because this often induces uncontrollable shivering, with a considerable increase in the rate of heat production, others have suggested that sponge or spray cooling of the skin is likely to be more effective for rapidly decreasing the body core temperature.

Harmful Effects of High Temperature. The pathological findings in a person who dies of hyperpyrexia are local

hemorrhages and parenchymatous degeneration of cells throughout the entire body, but especially in the brain. Once neuronal cells are destroyed, they can never be replaced. Also, damage to the liver, kidneys, and other organs can often be severe enough that failure of one or more of these organs eventually causes death, but sometimes not until several days after the heatstroke.

Acclimatization to Heat. It can be extremely important to acclimatize people to extreme heat. Examples of people requiring acclimatization are soldiers on duty in the tropics and miners working in the 2-mile-deep gold mines of South Africa, where the temperature approaches body temperature and the humidity approaches 100 percent. A person exposed to heat for several hours each day while performing a reasonably heavy workload will develop increased tolerance to hot and humid conditions in 1 to 3 weeks.

Among the most important physiological changes that occur during this acclimatization process are an approximately twofold increase in the maximum rate of sweating, an increase in plasma volume, and diminished loss of salt in the sweat and urine to almost none; the last two effects result from increased secretion of aldosterone by the adrenal glands.

Exposure of the Body to Extreme Cold

Unless treated immediately, a person exposed to ice water for 20 to 30 minutes ordinarily dies because of heart standstill or heart fibrillation. By that time, the internal body temperature will have fallen to about 77°F. If warmed rapidly by the application of external heat, the person's life can often be saved.

Loss of Temperature Regulation at Low Temperatures. As noted in Figure 73-10, once the body temperature has fallen below about 85°F, the ability of the hypothalamus to regulate temperature is lost; it is greatly impaired even when the body temperature falls below about 94°F. Part of the reason for this diminished temperature regulation is that the rate of chemical heat production in each cell is depressed almost twofold for each 10°F decrease in body temperature. Also, sleepiness develops (later followed by coma), which depresses the activity of the central nervous system heat control mechanisms and prevents shivering.

Frostbite. When the body is exposed to extremely low temperatures, surface areas can freeze; the freezing is called *frostbite*. This occurs especially in the lobes of the ears and in the digits of the hands and feet. If the freeze has been sufficient to cause extensive formation of ice crystals in the cells, permanent damage usually results, such as permanent circulatory impairment and local tissue damage. Often gangrene follows thawing, and the frostbitten areas must be removed surgically.

Cold-Induced Vasodilation Is a Final Protection Against Frostbite at Almost Freezing Temperatures. When the temperature of tissues falls almost to freezing, the smooth muscle in the vascular wall becomes paralyzed because of the cold itself, and sudden vasodilation occurs, often manifested by a flush of the skin. This mechanism helps prevent frostbite by delivering warm blood to the skin. This mechanism is far less developed in humans than in most lower animals that live in the cold all the time.

Artificial Hypothermia. It is easy to decrease the temperature of a person by first administering a strong sedative to depress the reactivity of the hypothalamic temperature controller and then cooling the person with ice or cooling blankets until the temperature falls. The temperature can then be maintained below 90°F for several days to a week or more by continual sprinkling of cool water or alcohol on the body. Such artificial cooling has been used during heart surgery so that the heart can be stopped artificially for many minutes at a time. Cooling to this extent does not cause tissue damage, but it does slow the heart and greatly depresses cell metabolism so that the body's cells can survive 30 minutes to more than 1 hour without blood flow during the surgical procedure.

Bibliography

Aronoff DM, Neilson EG: Antipyretics: mechanisms of action and clinical use in fever suppression, *Am J Med* 111:304, 2001.

Benarroch EE: Thermoregulation: recent concepts and remaining questions, *Neurology* 69:1293, 2007.

Blatteis CM: Endotoxic fever: new concepts of its regulation suggest new approaches to its management, *Pharmacol Ther* 111:194, 2006.

Blatteis CM: The onset of fever: new insights into its mechanism, *Prog Brain Res* 162:3, 2007.

Conti B, Tabarean I, Andrei C, Bartfai T: Cytokines and fever, *Front Biosci* 9:1433, 2004.

Florez-Duquet M, McDonald RB: Cold-induced thermoregulation and biological aging, *Physiol Rev* 78:339, 1998.

González-Alonso J, Crandall CG, Johnson JM: The cardiovascular challenge of exercising in the heat, *J Physiol* 586:45, 2008.

Horowitz M: Matching the heart to heat-induced circulatory load: heat-acclimatory responses, *News Physiol Sci* 18:215, 2003.

Katschinski DM: On heat and cells and proteins, *News Physiol Sci* 19:11, 2004.

Kenney WL, Munce TA: Aging and human temperature regulation, *J Appl Physiol* 95:2598, 2003.

Kozak W, Kluger MJ, Tesfaigzi J, et al: Molecular mechanisms of fever and endogenous antipyresis, *Ann N Y Acad Sci* 917:121, 2000.

Morrison SF: Central pathways controlling brown adipose tissue thermogenesis, *News Physiol Sci* 19:67, 2004.

Morrison SF, Nakamura K, Madden CJ: Central control of thermogenesis in mammals, *Exp Physiol* 93:773, 2008.

Olsen TS, Weber UJ, Kammersgaard LP: Therapeutic hypothermia for acute stroke, *Lancet Neurol* 2:410, 2003.

Romanovsky AA: Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system, *Am J Physiol Regul Integr Comp Physiol* 292:R37, 2007.

Rowland T: Thermoregulation during exercise in the heat in children: old concepts revisited, *J Appl Physiol* 105:718, 2008.

Saper CB: Neurobiological basis of fever, *Ann N Y Acad Sci* 856:90, 1998.

Simon A, van der Meer JW: Pathogenesis of familial periodic fever syndromes or hereditary autoinflammatory syndromes, *Am J Physiol Regul Integr Comp Physiol* 292:R86, 2007.

Steinman L: Nuanced roles of cytokines in three major human brain disorders, *J Clin Invest* 118:3557, 2008.

CHAPTER 74

Introduction to Endocrinology

Coordination of Body Functions by Chemical Messengers

The multiple activities of the cells, tissues, and organs of the body are coordinated by the interplay of several types of chemical messenger systems:

1. *Neurotransmitters* are released by axon terminals of neurons into the synaptic junctions and act locally to control nerve cell functions.
2. *Endocrine hormones* are released by glands or specialized cells into the circulating blood and influence the function of target cells at another location in the body.
3. *Neuroendocrine hormones* are secreted by neurons into the circulating blood and influence the function of target cells at another location in the body.
4. *Paracrines* are secreted by cells into the extracellular fluid and affect neighboring target cells of a different type.
5. *Autocrines* are secreted by cells into the extracellular fluid and affect the function of the same cells that produced them.
6. *Cytokines* are peptides secreted by cells into the extracellular fluid and can function as autocrines, paracrines, or endocrine hormones. Examples of cytokines include the *interleukins* and other *lymphokines* that are secreted by helper cells and act on other cells of the immune system (see Chapter 34). Cytokine hormones (e.g., *leptin*) produced by adipocytes are sometimes called *adipokines*.

In the next few chapters, we discuss mainly the endocrine and neuroendocrine hormone systems, keeping in mind that many of the body's chemical messenger systems interact with one another to maintain homeostasis. For example, the adrenal medullae and the pituitary gland secrete their hormones primarily in response to neural stimuli. The neuroendocrine cells, located in the hypothalamus, have axons that terminate in the posterior pituitary gland and median eminence and secrete several neurohormones, including *antidiuretic hormone* (ADH), *oxytocin,* and *hypophysiotropic hormones,* which control the secretion of anterior pituitary hormones.

The *endocrine hormones* are carried by the circulatory system to cells throughout the body, including the nervous system in some cases, where they bind with receptors and initiate many cell reactions. Some endocrine hormones affect many different types of cells of the body; for example, *growth hormone* (from the anterior pituitary gland) causes growth in most parts of the body, and *thyroxine* (from the thyroid gland) increases the rate of many chemical reactions in almost all the body's cells.

Other hormones affect mainly specific *target tissues* because these tissues have abundant receptors for the hormone. For example, *adrenocorticotropic hormone* (ACTH) from the anterior pituitary gland specifically stimulates the adrenal cortex, causing it to secrete adrenocortical hormones, and the *ovarian hormones* have their main effects on the female sex organs and the secondary sexual characteristics of the female body.

Figure 74-1 shows the anatomical loci of the major endocrine glands and endocrine tissues of the body, except for the placenta, which is an additional source of the sex hormones. Table 74-1 provides an overview of the different hormone systems and their most important actions.

The multiple hormone systems play a key role in regulating almost all body functions, including metabolism, growth and development, water and electrolyte balance, reproduction, and behavior. For instance, without growth hormone, a person would be a dwarf. Without thyroxine and triiodothyronine from the thyroid gland, almost all the chemical reactions of the body would become sluggish and the person would become sluggish as well. Without insulin from the pancreas, the body's cells could use little of the food carbohydrates for energy. And without the sex hormones, sexual development and sexual functions would be absent.

Chemical Structure and Synthesis of Hormones

Three general classes of hormones exist:

1. *Proteins and polypeptides,* including hormones secreted by the anterior and posterior pituitary gland, the pancreas (insulin and glucagon), the parathyroid gland (parathyroid hormone), and many others (see Table 74-1).

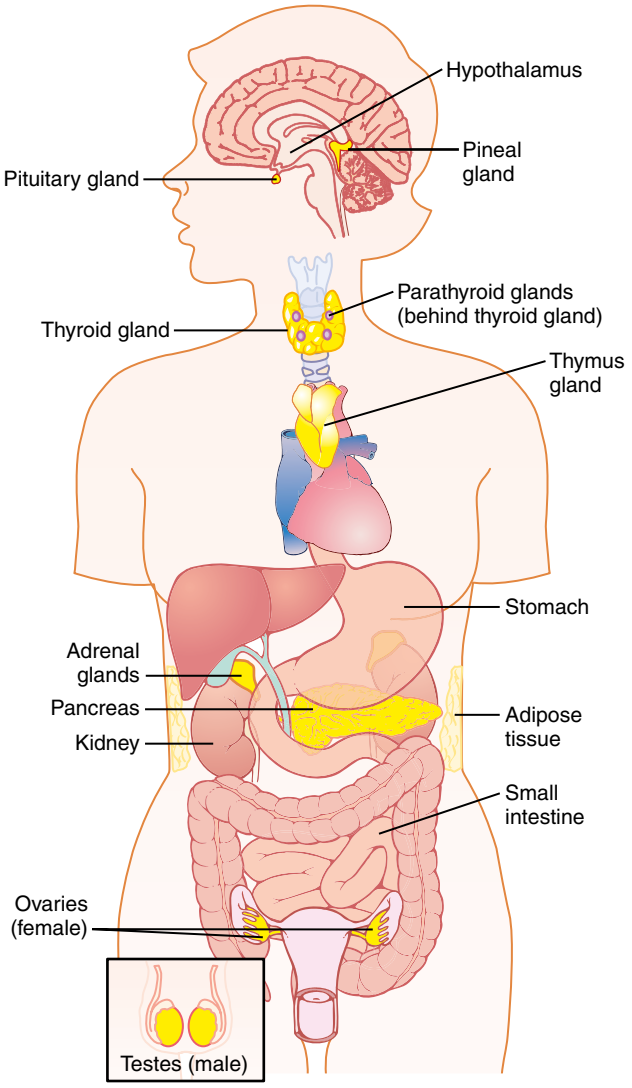


Figure 74-1 Anatomical loci of the principal endocrine glands and tissues of the body.

2. *Steroids* secreted by the adrenal cortex (cortisol and aldosterone), the ovaries (estrogen and progesterone), the testes (testosterone), and the placenta (estrogen and progesterone).
3. *Derivatives of the amino acid tyrosine,* secreted by the thyroid (thyroxine and triiodothyronine) and the adrenal medullae (epinephrine and norepinephrine). There are no known polysaccharides or nucleic acid hormones.

Polypeptide and Protein Hormones Are Stored in Secretory Vesicles Until Needed. Most of the hormones in the body are polypeptides and proteins. These hormones range in size from small peptides with as few as 3 amino acids (thyrotropin-releasing hormone) to proteins with almost 200 amino acids (growth hormone and prolactin). In general, polypeptides with 100 or more amino acids are called *proteins,* and those with fewer than 100 amino acids are referred to as *peptides.*

Protein and peptide hormones are synthesized on the rough end of the endoplasmic reticulum of the different endocrine cells, in the same fashion as most other proteins (Figure 74-2). They are usually synthesized first as larger proteins that are not biologically active *(preprohormones)* and are cleaved to form smaller *prohormones* in the endoplasmic reticulum. These are then transferred to the Golgi apparatus for packaging into secretory vesicles. In this process, enzymes in the vesicles cleave the prohormones to produce smaller, biologically active hormones and inactive fragments. The vesicles are stored within the cytoplasm, and many are bound to the cell membrane until their secretion is needed. Secretion of the hormones (as well as the inactive fragments) occurs when the secretory vesicles fuse with the cell membrane and the granular contents are extruded into the interstitial fluid or directly into the blood stream by *exocytosis.*

In many cases, the stimulus for exocytosis is an increase in cytosolic calcium concentration caused by depolarization of the plasma membrane. In other instances, stimulation of an endocrine cell surface receptor causes increased cyclic adenosine monophosphate (cAMP) and subsequently activation of protein kinases that initiate secretion of the hormone. The peptide hormones are water soluble, allowing them to enter the circulatory system easily, where they are carried to their target tissues.

Steroid Hormones Are Usually Synthesized from Cholesterol and Are Not Stored. The chemical structure of steroid hormones is similar to that of cholesterol, and in most instances hormones are synthesized from cholesterol itself. They are lipid soluble and consist of three cyclohexyl rings and one cyclopentyl ring combined into a single structure (Figure 74-3).

Although there is usually very little hormone storage in steroid-producing endocrine cells, large stores of cholesterol esters in cytoplasm vacuoles can be rapidly mobilized for steroid synthesis after a stimulus. Much of the cholesterol in steroid-producing cells comes from the plasma, but there is also de novo synthesis of cholesterol in steroid-producing cells. Because the steroids are highly lipid soluble, once they are synthesized, they simply diffuse across the cell membrane and enter the interstitial fluid and then the blood.

Amine Hormones Are Derived from Tyrosine. The two groups of hormones derived from tyrosine, the thyroid and the adrenal medullary hormones, are formed by the actions of enzymes in the cytoplasmic compartments of the glandular cells. The thyroid hormones are synthesized and stored in the thyroid gland and incorporated into macromolecules of the protein *thyroglobulin,* which is stored in large follicles within the thyroid gland. Hormone secretion occurs when the amines are split from thyroglobulin, and the free hormones are then released into the blood stream. After entering the blood, most of the thyroid hormones combine with plasma proteins, especially *thyroxine-binding globulin,* which slowly releases the hormones to the target tissues.

Table 74-1 Endocrine Glands, Hormones, and Their Functions and Structure

Gland/Tissue	Hormones	Major Functions	Chemical Structure
Hypothalamus (Chapter 75)	Thyrotropin-releasing hormone (TRH)	Stimulates secretion of thyroid-stimulating hormone (TSH) and prolactin	Peptide
	Corticotropin-releasing hormone (CRH)	Causes release of adrenocorticotropic hormone (ACTH)	Peptide
	Growth hormone–releasing hormone (GHRH)	Causes release of growth hormone	Peptide
	Growth hormone inhibitory hormone (GHIH) (somatostatin)	Inhibits release of growth hormone	Peptide
	Gonadotropin-releasing hormone (GnRH)	Causes release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)	
	Dopamine or prolactin-inhibiting factor (PIF)	Inhibits release of prolactin	Amine
Anterior pituitary (Chapter 75)	Growth hormone	Stimulates protein synthesis and overall growth of most cells and tissues	Peptide
	TSH	Stimulates synthesis and secretion of thyroid hormones (thyroxine and triiodothyronine)	Peptide
	ACTH	Stimulates synthesis and secretion of adrenocortical hormones (cortisol, androgens, and aldosterone)	Peptide
	Prolactin	Promotes development of the female breasts and secretion of milk	Peptide
	FSH	Causes growth of follicles in the ovaries and sperm maturation in Sertoli cells of testes	Peptide
	LH	Stimulates testosterone synthesis in Leydig cells of testes; stimulates ovulation, formation of corpus luteum, and estrogen and progesterone synthesis in ovaries	Peptide
Posterior pituitary (Chapter 75)	Antidiuretic hormone (ADH) (also called *vasopressin*)	Increases water reabsorption by the kidneys and causes vasoconstriction and increased blood pressure	Peptide
	Oxytocin	Stimulates milk ejection from breasts and uterine contractions	Peptide
Thyroid (Chapter 76)	Thyroxine (T_4) and triiodothyronine (T_3)	Increases the rates of chemical reactions in most cells, thus increasing body metabolic rate	Amine
	Calcitonin	Promotes deposition of calcium in the bones and decreases extracellular fluid calcium ion concentration	Peptide
Adrenal cortex (Chapter 77)	Cortisol	Has multiple metabolic functions for controlling metabolism of proteins, carbohydrates, and fats; also has anti-inflammatory effects	Steroid
	Aldosterone	Increases renal sodium reabsorption, potassium secretion, and hydrogen ion secretion	Steroid
Adrenal medulla (Chapter 60)	Norepinephrine, epinephrine	Same effects as sympathetic stimulation	Amine
Pancreas (Chapter 78)	Insulin (β cells)	Promotes glucose entry in many cells, and in this way controls carbohydrate metabolism	Peptide

(Continued)

Table 74-1 Endocrine Glands, Hormones, and Their Functions and Structure—Cont'd

Gland/Tissue	Hormones	Major Functions	Chemical Structure
	Glucagon (α cells)	Increases synthesis and release of glucose from the liver into the body fluids	Peptide
Parathyroid (Chapter 79)	Parathyroid hormone (PTH)	Controls serum calcium ion concentration by increasing calcium absorption by the gut and kidneys and releasing calcium from bones	Peptide
Testes (Chapter 80)	Testosterone	Promotes development of male reproductive system and male secondary sexual characteristics	Steroid
Ovaries (Chapter 81)	Estrogens	Promotes growth and development of female reproductive system, female breasts, and female secondary sexual characteristics	Steroid
	Progesterone	Stimulates secretion of "uterine milk" by the uterine endometrial glands and promotes development of secretory apparatus of breasts	Steroid
Placenta (Chapter 82)	Human chorionic gonadotropin (HCG)	Promotes growth of corpus luteum and secretion of estrogens and progesterone by corpus luteum	Peptide
	Human somatomammotropin	Probably helps promote development of some fetal tissues as well as the mother's breasts	Peptide
	Estrogens	See actions of estrogens from ovaries	Steroid
	Progesterone	See actions of progesterone from ovaries	Steroid
Kidney (Chapter 26)	Renin	Catalyzes conversion of angiotensinogen to angiotensin I (acts as an enzyme)	Peptide
	1,25-Dihydroxycholecalciferol	Increases intestinal absorption of calcium and bone mineralization	Steroid
	Erythropoietin	Increases erythrocyte production	Peptide
Heart (Chapter 22)	Atrial natriuretic peptide (ANP)	Increases sodium excretion by kidneys, reduces blood pressure	Peptide
Stomach (Chapter 64)	Gastrin	Stimulates HCl secretion by parietal cells	Peptide
Small intestine (Chapter 64)	Secretin	Stimulates pancreatic acinar cells to release bicarbonate and water	Peptide
	Cholecystokinin (CCK)	Stimulates gallbladder contraction and release of pancreatic enzymes	Peptide
Adipocytes (Chapter 71)	Leptin	Inhibits appetite, stimulates thermogenesis	Peptide

Epinephrine and norepinephrine are formed in the adrenal medulla, which normally secretes about four times more epinephrine than norepinephrine. Catecholamines are taken up into preformed vesicles and stored until secreted. Similar to the protein hormones stored in secretory granules, catecholamines are also released from adrenal medullary cells by exocytosis. Once the catecholamines enter the circulation, they can exist in the plasma in free form or in conjugation with other substances.

Hormone Secretion, Transport, and Clearance from the Blood

Onset of Hormone Secretion After a Stimulus, and Duration of Action of Different Hormones. Some hormones, such as norepinephrine and epinephrine, are secreted within seconds after the gland is stimulated, and they may develop full action within another few seconds to minutes; the actions of other hormones, such as thyroxine or growth hormone, may require months for full effect. Thus, each of the different hormones has its own characteristic onset and duration of action—each tailored to perform its specific control function.

Concentrations of Hormones in the Circulating Blood, and Hormonal Secretion Rates. The concentrations of hormones required to control most metabolic and endocrine functions are incredibly small. Their concentrations in the blood range from as little as 1 picogram (which is one millionth of one millionth of a gram) in each milliliter of blood up to at most a few micrograms (a few millionths of a gram) per milliliter of blood. Similarly, the rates of secretion of the various hormones are extremely small, usually measured in micrograms or milligrams per day. We shall see later in this

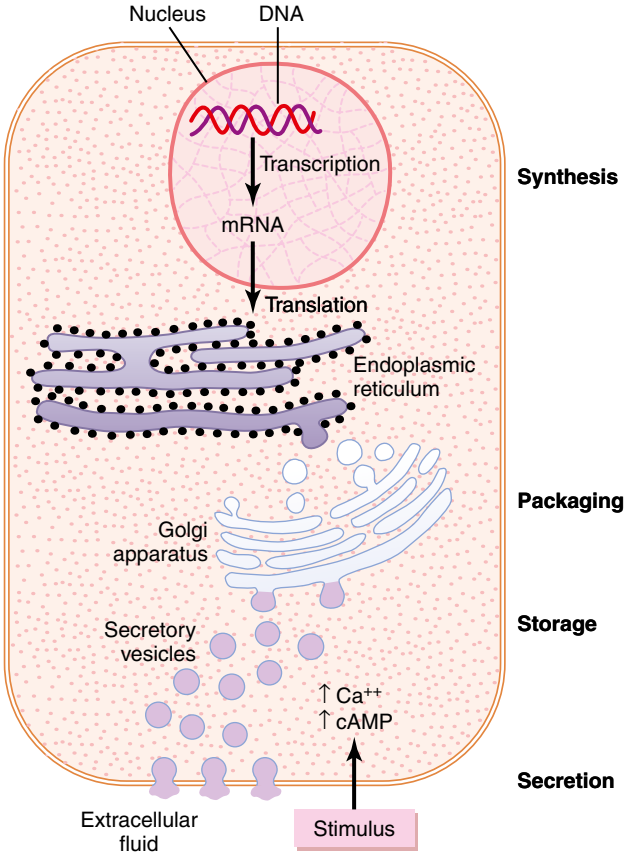


Figure 74-2 Synthesis and secretion of peptide hormones. The stimulus for hormone secretion often involves changes in intracellular calcium or changes in cyclic adenosine monophosphate (cAMP) in the cell.

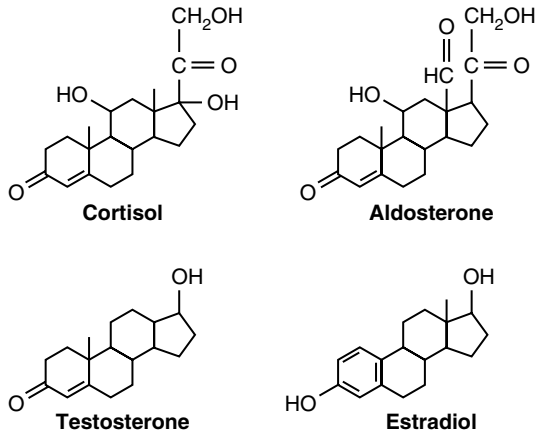


Figure 74-3 Chemical structures of several steroid hormones.

chapter that highly specialized mechanisms are available in the target tissues that allow even these minute quantities of hormones to exert powerful control over the physiological systems.

Feedback Control of Hormone Secretion

Negative Feedback Prevents Overactivity of Hormone Systems. Although the plasma concentrations of many hormones fluctuate in response to various stimuli that occur throughout the day, all hormones studied thus far appear to be closely controlled. In most instances, this control is exerted through *negative feedback mechanisms* that ensure a proper level of hormone activity at the target tissue. After a stimulus causes release of the hormone, conditions or products resulting from the action of the hormone tend to suppress its further release. In other words, the hormone (or one of its products) has a negative feedback effect to prevent oversecretion of the hormone or overactivity at the target tissue.

The controlled variable is sometimes not the secretory rate of the hormone itself but the degree of activity of the target tissue. Therefore, only when the target tissue activity rises to an appropriate level will feedback signals to the endocrine gland become powerful enough to slow further secretion of the hormone. Feedback regulation of hormones can occur at all levels, including gene transcription and translation steps involved in the synthesis of hormones and steps involved in processing hormones or releasing stored hormones.

Surges of Hormones Can Occur with Positive Feedback. In a few instances, *positive feedback* occurs when the biological action of the hormone causes additional secretion of the hormone. One example of this is the surge of *luteinizing hormone* (LH) that occurs as a result of the stimulatory effect of estrogen on the anterior pituitary before ovulation. The secreted LH then acts on the ovaries to stimulate additional secretion of estrogen, which in turn causes more secretion of LH. Eventually, LH reaches an appropriate concentration and typical negative feedback control of hormone secretion is then exerted.

Cyclical Variations Occur in Hormone Release. Superimposed on the negative and positive feedback control of hormone secretion are periodic variations in hormone release that are influenced by seasonal changes, various stages of development and aging, the diurnal (daily) cycle, and sleep. For example, the secretion of growth hormone is markedly increased during the early period of sleep but is reduced during the later stages of sleep. In many cases, these cyclical variations in hormone secretion are due to changes in activity of neural pathways involved in controlling hormone release.

Transport of Hormones in the Blood

Water-soluble hormones (peptides and catecholamines) are dissolved in the plasma and transported from their sites of synthesis to target tissues, where they diffuse out of the capillaries, into the interstitial fluid, and ultimately to target cells.

Steroid and thyroid hormones, in contrast, circulate in the blood mainly bound to plasma proteins. Usually less than 10 percent of steroid or thyroid hormones in the plasma exist free in solution. For example, more than 99 percent of the thyroxine in the blood is bound to plasma proteins. However, protein-bound hormones cannot easily diffuse across the capillaries and gain access to their

target cells and are therefore biologically inactive until they dissociate from plasma proteins.

The relatively large amounts of hormones bound to proteins serve as reservoirs, replenishing the concentration of free hormones when they are bound to target receptors or lost from the circulation. Binding of hormones to plasma proteins greatly slows their clearance from the plasma.

"Clearance" of Hormones from the Blood

Two factors can increase or decrease the concentration of a hormone in the blood. One of these is the rate of hormone secretion into the blood. The second is the rate of removal of the hormone from the blood, which is called the *metabolic clearance rate.* This is usually expressed in terms of the number of milliliters of plasma cleared of the hormone per minute. To calculate this clearance rate, one measures (1) the rate of disappearance of the hormone from the plasma (e.g., nanograms per minute) and (2) the plasma concentration of the hormone (e.g., nanograms per milliliter of plasma). Then, the metabolic clearance rate is calculated by the following formula:

$$\text{Metabolic clearance rate} = \frac{\text{Rate of disappearance of hormone from the plasma}}{\text{Concentration of hormone}}$$

The usual procedure for making this measurement is the following: A purified solution of the hormone to be measured is tagged with a radioactive substance. Then the radioactive hormone is infused at a constant rate into the blood stream until the radioactive concentration in the plasma becomes steady. At this time, the rate of disappearance of the radioactive hormone from the plasma equals the rate at which it is infused, which gives one the rate of disappearance. At the same time, the plasma concentration of the radioactive hormone is measured using a standard radioactive counting procedure. Then, using the formula just cited, the metabolic clearance rate is calculated.

Hormones are "cleared" from the plasma in several ways, including (1) metabolic destruction by the tissues, (2) binding with the tissues, (3) excretion by the liver into the bile, and (4) excretion by the kidneys into the urine. For certain hormones, a decreased metabolic clearance rate may cause an excessively high concentration of the hormone in the circulating body fluids. For instance, this occurs for several of the steroid hormones when the liver is diseased because these hormones are conjugated mainly in the liver and then "cleared" into the bile.

Hormones are sometimes degraded at their target cells by enzymatic processes that cause endocytosis of the cell membrane hormone-receptor complex; the hormone is then metabolized in the cell, and the receptors are usually recycled back to the cell membrane.

Most of the peptide hormones and catecholamines are water soluble and circulate freely in the blood. They are usually degraded by enzymes in the blood and tissues and rapidly excreted by the kidneys and liver, thus remaining in the blood for only a short time. For example, the half-life of angiotensin II circulating in the blood is less than a minute.

Hormones that are bound to plasma proteins are cleared from the blood at much slower rates and may remain in the circulation for several hours or even days. The half-life of adrenal steroids in the circulation, for example, ranges between 20 and 100 minutes, whereas the half-life of the protein-bound thyroid hormones may be as long as 1 to 6 days.

Mechanisms of Action of Hormones

Hormone Receptors and Their Activation

The first step of a hormone's action is to bind to specific *receptors* at the target cell. Cells that lack receptors for the hormones do not respond. Receptors for some hormones are located on the target cell membrane, whereas other hormone receptors are located in the cytoplasm or the nucleus. When the hormone combines with its receptor, this usually initiates a cascade of reactions in the cell, with each stage becoming more powerfully activated so that even small concentrations of the hormone can have a large effect.

Hormonal receptors are large proteins, and each cell that is to be stimulated usually has some 2000 to 100,000 receptors. Also, each receptor is usually highly specific for a single hormone; this determines the type of hormone that will act on a particular tissue. The target tissues that are affected by a hormone are those that contain its specific receptors.

The locations for the different types of hormone receptors are generally the following:

1. *In or on the surface of the cell membrane.* The membrane receptors are specific mostly for the protein, peptide, and catecholamine hormones.
2. *In the cell cytoplasm.* The primary receptors for the different steroid hormones are found mainly in the cytoplasm.
3. *In the cell nucleus.* The receptors for the thyroid hormones are found in the nucleus and are believed to be located in direct association with one or more of the chromosomes.

The Number and Sensitivity of Hormone Receptors Are Regulated. The number of receptors in a target cell usually does not remain constant from day to day, or even from minute to minute. The receptor proteins themselves are often inactivated or destroyed during the course of their function, and at other times they are reactivated or new ones are manufactured by the protein-manufacturing mechanism of the cell. For instance, increased hormone concentration and increased binding with its target cell receptors sometimes cause the number of active receptors to decrease. This *down-regulation* of the receptors can occur as a result of (1) inactivation of some of the receptor molecules; (2) inactivation of some of the intracellular

protein signaling molecules; (3) temporary sequestration of the receptor to the inside of the cell, away from the site of action of hormones that interact with cell membrane receptors; (4) destruction of the receptors by lysosomes after they are internalized; or (5) decreased production of the receptors. In each case, receptor down-regulation decreases the target tissue's responsiveness to the hormone.

Some hormones cause *up-regulation* of receptors and intracellular signaling proteins; that is, the stimulating hormone induces greater than normal formation of receptor or intracellular signaling molecules by the protein-manufacturing machinery of the target cell, or greater availability of the receptor for interaction with the hormone. When this occurs, the target tissue becomes progressively more sensitive to the stimulating effects of the hormone.

Intracellular Signaling After Hormone Receptor Activation

Almost without exception, a hormone affects its target tissues by first forming a hormone-receptor complex. This alters the function of the receptor itself, and the activated receptor initiates the hormonal effects. To explain this, let us give a few examples of the different types of interactions.

Ion Channel–Linked Receptors. Virtually all the neurotransmitter substances, such as acetylcholine and norepinephrine, combine with receptors in the postsynaptic membrane. This almost always causes a change in the structure of the receptor, usually opening or closing a channel for one or more ions. Some of these *ion channel–linked receptors* open (or close) channels for sodium ions, others for potassium ions, others for calcium ions, and so forth. The altered movement of these ions through the channels causes the subsequent effects on the postsynaptic cells. Although a few hormones may exert some of their actions through activation of ion channel receptors, most hormones that open or close ions channels do this indirectly by coupling with G protein–linked or enzyme-linked receptors, as discussed next.

G Protein–Linked Hormone Receptors. Many hormones activate receptors that indirectly regulate the activity of target proteins (e.g., enzymes or ion channels) by coupling with groups of cell membrane proteins called *heterotrimeric GTP-binding proteins (G proteins)* (Figure 74-4). Of more than 1000 known G protein–coupled receptors, all have seven transmembrane segments that loop in and out of the cell membrane. Some parts of the receptor that protrude into the cell cytoplasm (especially the cytoplasmic tail of the receptor) are coupled to G proteins that include three (i.e., trimeric) parts—the α, β, and γ subunits. When the ligand (hormone) binds to the extracellular part of the receptor, a conformational change occurs in the receptor that activates the G proteins and induces intracellular signals that either (1) open or close cell membrane ion channels or (2) change the activity of an enzyme in the cytoplasm of the cell.

The trimeric G proteins are named for their ability to bind *guanosine nucleotides.* In their inactive state, the α, β, and γ subunits of G proteins form a complex that binds *guanosine diphosphate* (GDP) on the α subunit. When the receptor is activated, it undergoes a conformational change that causes the GDP-bound trimeric G protein to associate with the cytoplasmic part of the receptor and to exchange GDP for *guanosine triphosphate* (GTP). Displacement of GDP by GTP causes the α subunit to dissociate from the trimeric complex and to associate with other intracellular signaling proteins; these proteins, in turn, alter the activity of ion channels or intracellular enzymes such as *adenylyl cyclase* or *phospholipase C,* which alters cell function.

The signaling event is terminated when the hormone is removed and the α subunit inactivates itself by converting its bound GTP to GDP; then the α subunit once again combines with the β and γ subunits to form an inactive, membrane-bound trimeric G protein.

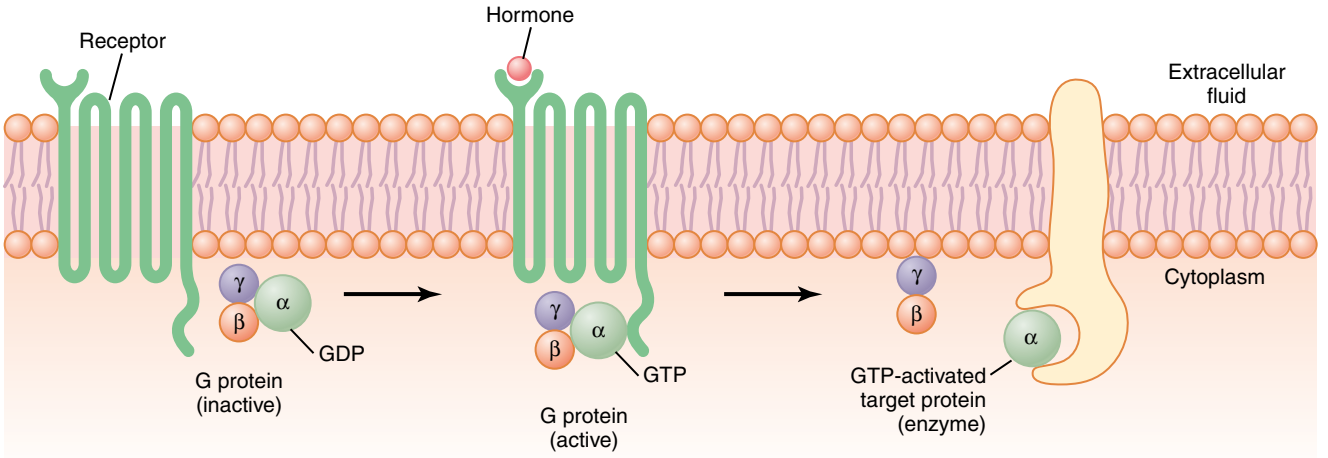


Figure 74-4 Mechanism of activation of a G protein–coupled receptor. When the hormone activates the receptor, the inactive α, β, and γ G protein complex associates with the receptor and is activated, with an exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP). This causes the α subunit (to which the GTP is bound) to dissociate from the β and γ subunits of the G protein and to interact with membrane-bound target proteins (enzymes) that initiate intracellular signals.

Some hormones are coupled to *inhibitory G proteins* (denoted G_i proteins), whereas others are coupled to *stimulatory G proteins* (denoted G_s proteins). Thus, depending on the coupling of a hormone receptor to an inhibitory or stimulatory G protein, a hormone can either increase or decrease the activity of intracellular enzymes. This complex system of cell membrane G proteins provides a vast array of potential cell responses to different hormones in the various target tissues of the body.

Enzyme-Linked Hormone Receptors. Some receptors, when activated, function directly as enzymes or are closely associated with enzymes that they activate. These *enzyme-linked receptors* are proteins that pass through the membrane only once, in contrast to the seven-transmembrane G protein–coupled receptors. Enzyme-linked receptors have their hormone-binding site on the outside of the cell membrane and their catalytic or enzyme-binding site on the inside. When the hormone binds to the extracellular part of the receptor, an enzyme immediately inside the cell membrane is activated (or occasionally inactivated). Although many enzyme-linked receptors have intrinsic enzyme activity, others rely on enzymes that are closely associated with the receptor to produce changes in cell function.

One example of an enzyme-linked receptor is the *leptin receptor* (Figure 74-5). Leptin is a hormone secreted by fat cells and has many physiological effects, but it is especially important in regulating appetite and energy balance, as discussed in Chapter 71. The leptin receptor is a member of a large family of *cytokine receptors* that do not themselves contain enzymatic activity but signal through associated enzymes. In the case of the leptin receptor, one of the signaling pathways occurs through a *tyrosine kinase* of the *janus kinase* (JAK) family, *JAK2.* The leptin receptor exists as a dimer (i.e., in two parts), and binding of leptin to the extracellular part of the receptor alters its conformation, enabling phosphorylation and activation of the intracellular associated JAK2 molecules. The activated JAK2 molecules then phosphorylate other tyrosine residues within the leptin receptor–JAK2 complex to mediate intracellular signaling. The intracellular signals include phosphorylation of *signal transducer and activator of transcription* (STAT) proteins, which activates transcription by leptin target genes to initiate protein synthesis. Phosphorylation of JAK2 also leads to activation of other intracellular enzyme pathways such as *mitogen-activated protein kinases* (MAPK) and *phosphatidylinositol 3-kinase* (PI3K). Some of the effects of leptin occur rapidly as a result of activation of these intracellular enzymes, whereas other actions occur more slowly and require synthesis of new proteins.

Another example, one widely used in hormonal control of cell function, is for the hormone to bind with a special transmembrane receptor, which then becomes the activated enzyme *adenylyl cyclase* at the end that protrudes to the interior of the cell. This cyclase catalyzes

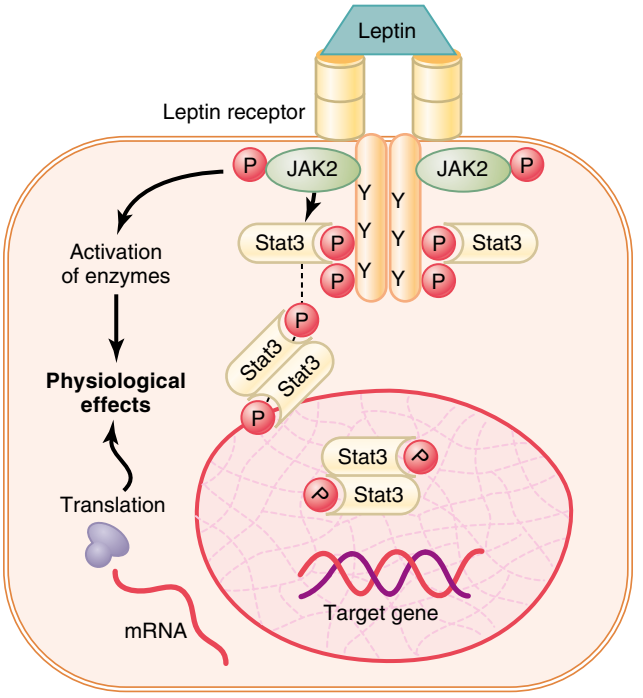


Figure 74-5 An enzyme-linked receptor—the leptin receptor. The receptor exists as a homodimer (two identical parts), and leptin binds to the extracellular part of the receptor, causing phosphorylation and activation of the intracellular associated janus kinase 2 (JAK2). This causes phosphorylation of signal transducer and activator of transcription (STAT) proteins, which then activates the transcription of target genes and the synthesis of proteins. JAK2 phosphorylation also activates several other enzyme systems that mediate some of the more rapid effects of leptin.

the formation of cAMP, which has a multitude of effects inside the cell to control cell activity, as discussed later. cAMP is called a *second messenger* because it is not the hormone itself that directly institutes the intracellular changes; instead, the cAMP serves as a second messenger to cause these effects.

For a few peptide hormones, such as atrial natriuretic peptide (ANP), *cyclic guanosine monophosphate* (cGMP), which is only slightly different from cAMP, serves in a similar manner as a second messenger.

Intracellular Hormone Receptors and Activation of Genes. Several hormones, including adrenal and gonadal steroid hormones, thyroid hormones, retinoid hormones, and vitamin D, bind with protein receptors inside the cell rather than in the cell membrane. Because these hormones are lipid soluble, they readily cross the cell membrane and interact with receptors in the cytoplasm or nucleus. The activated hormone-receptor complex then binds with a specific regulatory (promoter) sequence of the DNA called the *hormone response element,* and in this manner either activates or represses transcription of specific genes and formation of messenger RNA (mRNA) (Figure 74-6). Therefore, minutes, hours, or even days after the hormone has entered the cell, newly formed proteins appear in the cell and become the controllers of new or altered cellular functions.

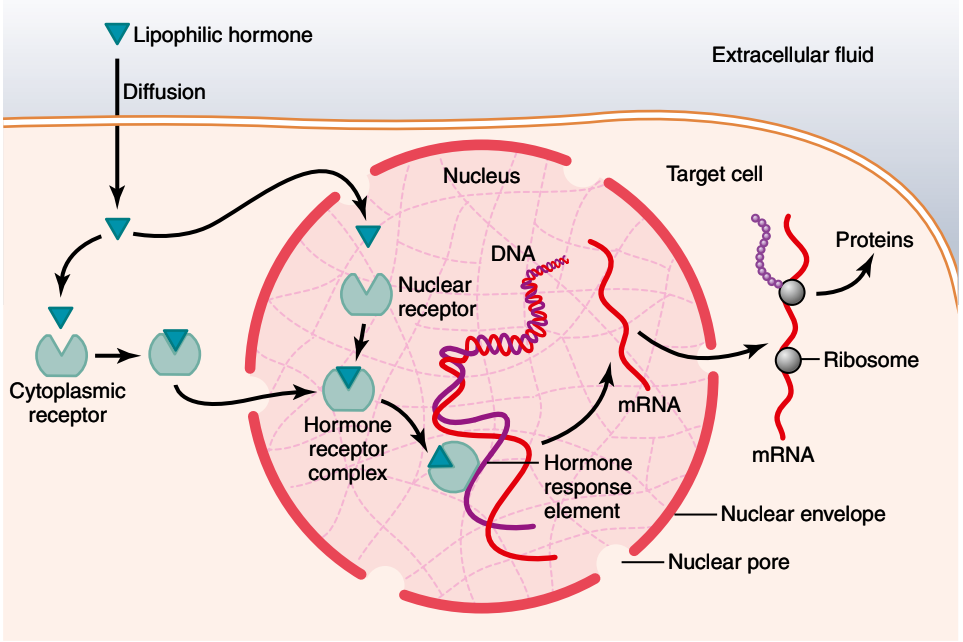


Figure 74-6 Mechanisms of interaction of lipophilic hormones, such as steroids, with intracellular receptors in target cells. After the hormone binds to the receptor in the cytoplasm or in the nucleus, the hormone-receptor complex binds to the hormone response element (promoter) on the DNA. This either activates or inhibits gene transcription, formation of messenger RNA (mRNA), and protein synthesis.

Many different tissues have identical intracellular hormone receptors, but the genes that the receptors regulate are different in the various tissues. An intracellular receptor can activate a gene response only if the appropriate combination of gene regulatory proteins is present, and many of these regulatory proteins are tissue specific. Thus, the responses of different tissues to a hormone are determined not only by the specificity of the receptors but also by the expression of genes that the receptor regulates.

Second Messenger Mechanisms for Mediating Intracellular Hormonal Functions

We noted earlier that one of the means by which hormones exert intracellular actions is to stimulate formation of the second messenger cAMP inside the cell membrane. The cAMP then causes subsequent intracellular effects of the hormone. Thus, the only direct effect that the hormone has on the cell is to activate a single type of membrane receptor. The second messenger does the rest.

cAMP is not the only second messenger used by the different hormones. Two other especially important ones are (1) calcium ions and associated *calmodulin* and (2) products of membrane phospholipid breakdown.

Adenylyl Cyclase–cAMP Second Messenger System

Table 74-2 shows a few of the many hormones that use the adenylyl cyclase-cAMP mechanism to stimulate their target tissues, and Figure 74-7 shows the adenylyl cyclase–cAMP second messenger system. Binding of the hormones with the receptor allows coupling of the receptor to a *G protein.* If the G protein stimulates the adenylyl cyclase–cAMP system, it is called a G_s *protein,* denoting a stimulatory G protein. Stimulation of adenylyl cyclase, a membrane-bound enzyme, by the G_s protein then catalyzes the conversion of a small amount of cytoplasmic *adenosine triphosphate* (ATP) into cAMP inside the cell. This then activates *cAMP-dependent protein kinase,* which phosphorylates specific proteins in the cell, triggering biochemical reactions that ultimately lead to the cell's response to the hormone.

Table 74-2 Hormones That Use the Adenylyl Cyclase–cAMP Second Messenger System

Adrenocorticotropic hormone (ACTH)
Angiotensin II (epithelial cells)
Calcitonin
Catecholamines (β receptors)
Corticotropin-releasing hormone (CRH)
Follicle-stimulating hormone (FSH)
Glucagon
Human chorionic gonadotropin (HCG)
Luteinizing hormone (LH)
Parathyroid hormone (PTH)
Secretin
Somatostatin
Thyroid-stimulating hormone (TSH)
Vasopressin (V_2 receptor, epithelial cells)

Once cAMP is formed inside the cell, it usually activates a *cascade of enzymes.* That is, first one enzyme is activated, which activates a second enzyme, which activates a third, and so forth. The importance of this mechanism is that only a few molecules of activated adenylyl cyclase immediately inside the cell membrane can cause many more molecules of the next enzyme to be activated, which can cause still more molecules of the third enzyme to be activated, and so forth. In this way, even the slightest amount of hormone acting on the cell surface can initiate a powerful cascading activating force for the entire cell.

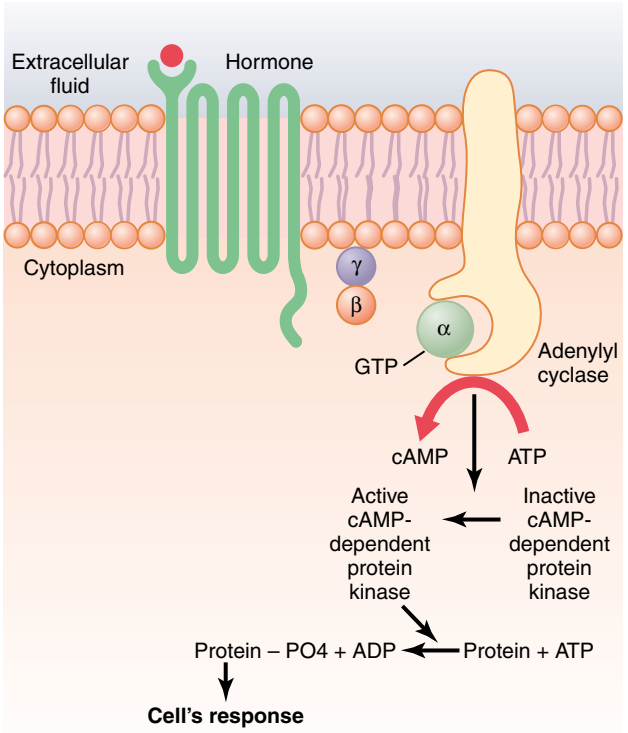


Figure 74-7 Cyclic adenosine monophosphate (cAMP) mechanism by which many hormones exert their control of cell function. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

If binding of the hormone to its receptors is coupled to an inhibitory G protein (denoted G_i protein), adenylyl cyclase will be inhibited, reducing the formation of cAMP and ultimately leading to an inhibitory action in the cell. Thus, depending on the coupling of the hormone receptor to an inhibitory or a stimulatory G protein, a hormone can either increase or decrease the concentration of cAMP and phosphorylation of key proteins inside the cell.

The specific action that occurs in response to increases or decreases of cAMP in each type of target cell depends on the nature of the intracellular machinery—some cells have one set of enzymes, and other cells have other enzymes. Therefore, different functions are elicited in different target cells, such as initiating synthesis of specific intracellular chemicals, causing muscle contraction or relaxation, initiating secretion by the cells, and altering cell permeability.

Thus, a thyroid cell stimulated by cAMP forms the metabolic hormones thyroxine and triiodothyronine, whereas the same cAMP in an adrenocortical cell causes secretion of the adrenocortical steroid hormones. In epithelial cells of the renal tubules, cAMP increases their permeability to water.

Cell Membrane Phospholipid Second Messenger System

Some hormones activate transmembrane receptors that activate the enzyme *phospholipase C* attached to the inside projections of the receptors (Table 74-3). This enzyme catalyzes the breakdown of some phospholipids in the cell membrane, especially *phosphatidylinositol bi-*

Table 74-3 Hormones That Use the Phospholipase C Second Messenger System

Angiotensin II (vascular smooth muscle)
Catecholamines (α receptors)
Gonadotropin-releasing hormone (GnRH)
Growth hormone–releasing hormone (GHRH)
Oxytocin
Thyrotropin releasing hormone (TRH)
Vasopressin (V1 receptor, vascular smooth muscle)

phosphate (PIP_2), into two different second messenger products: *inositol triphosphate* (IP_3) and *diacylglycerol* (DAG). The IP_3 mobilizes calcium ions from mitochondria and the endoplasmic reticulum, and the calcium ions then have their own second messenger effects, such as smooth muscle contraction and changes in cell secretion.

DAG, the other lipid second messenger, activates the enzyme *protein kinase C* (PKC), which then phosphorylates a large number of proteins, leading to the cell's response (Figure 74-8). In addition to these effects, the lipid portion of DAG is *arachidonic acid,* which is the precursor for the *prostaglandins* and other local hormones that cause multiple effects in tissues throughout the body.

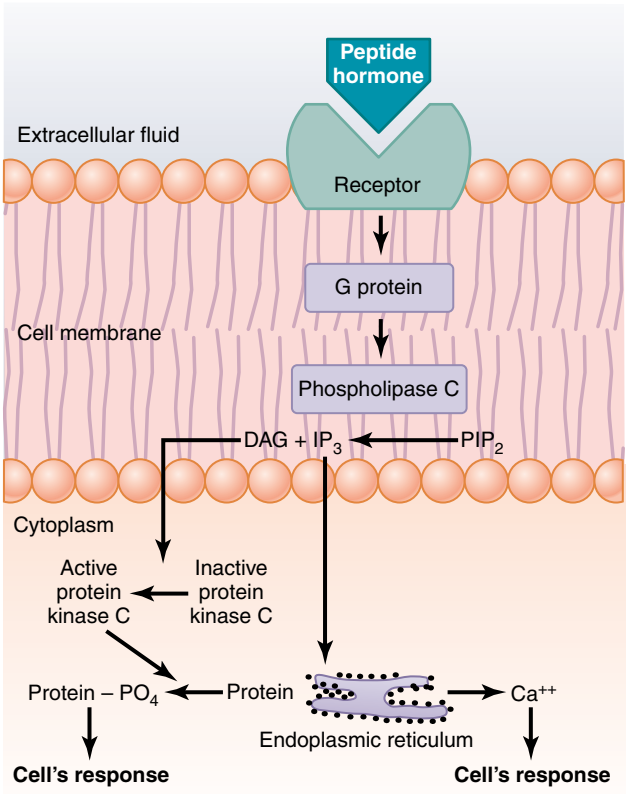


Figure 74-8 The cell membrane phospholipid second messenger system by which some hormones exert their control of cell function. DAG, diacylglycerol; IP_3, inositol triphosphate; PIP_2, phosphatidylinositol biphosphate.

Calcium-Calmodulin Second Messenger System

Another second messenger system operates in response to the entry of calcium into the cells. Calcium entry may be initiated by (1) changes in membrane potential that open calcium channels or (2) a hormone interacting with membrane receptors that open calcium channels.

On entering a cell, calcium ions bind with the protein *calmodulin.* This protein has four calcium sites, and when three or four of these sites have bound with calcium, the calmodulin changes its shape and initiates multiple effects inside the cell, including activation or inhibition of protein kinases. Activation of calmodulin-dependent protein kinases causes, via phosphorylation, activation or inhibition of proteins involved in the cell's response to the hormone. For example, one specific function of calmodulin is to activate *myosin light chain kinase,* which acts directly on the myosin of smooth muscle to cause smooth muscle contraction.

The normal calcium ion concentration in most cells of the body is 10^{-8} to 10^{-7} mol/L, which is not enough to activate the calmodulin system. But when the calcium ion concentration rises to 10^{-6} to 10^{-5} mol/L, enough binding occurs to cause all the intracellular actions of calmodulin. This is almost exactly the same amount of calcium ion change that is required in skeletal muscle to activate troponin C, which causes skeletal muscle contraction, as explained in Chapter 7. It is interesting that troponin C is similar to calmodulin in both function and protein structure.

Hormones That Act Mainly on the Genetic Machinery of the Cell

Steroid Hormones Increase Protein Synthesis

Another means by which hormones act—specifically, the steroid hormones secreted by the adrenal cortex, ovaries, and testes—is to cause synthesis of proteins in the target cells. These proteins then function as enzymes, transport proteins, or structural proteins, which in turn provide other functions of the cells.

The sequence of events in steroid function is essentially the following:

1. The steroid hormone diffuses across the cell membrane and enters the cytoplasm of the cell, where it binds with a specific *receptor protein.*
2. The combined receptor protein–hormone then diffuses into or is transported into the nucleus.
3. The combination binds at specific points on the DNA strands in the chromosomes, which activates the transcription process of specific genes to form mRNA.
4. The mRNA diffuses into the cytoplasm, where it promotes the translation process at the ribosomes to form new proteins.

To give an example, *aldosterone,* one of the hormones secreted by the adrenal cortex, enters the cytoplasm of renal tubular cells, which contain a specific receptor protein often called the *mineralocorticoid receptor.* Therefore, in these cells, the sequence of events cited earlier ensues. After about 45 minutes, proteins begin to appear in the renal tubular cells and promote sodium reabsorption from the tubules and potassium secretion into the tubules. Thus, the full action of the steroid hormone is characteristically delayed for at least 45 minutes—up to several hours or even days. This is in marked contrast to the almost instantaneous action of some of the peptide and amino acid–derived hormones, such as vasopressin and norepinephrine.

Thyroid Hormones Increase Gene Transcription in the Cell Nucleus

The thyroid hormones *thyroxine* and *triiodothyronine* cause increased transcription by specific genes in the nucleus. To accomplish this, these hormones first bind directly with receptor proteins in the nucleus; these receptors are *activated transcription factors* located within the chromosomal complex, and they control the function of the gene promoters, as explained in Chapter 3.

Two important features of thyroid hormone function in the nucleus are the following:

1. They activate the genetic mechanisms for the formation of many types of intracellular proteins—probably 100 or more. Many of these are enzymes that promote enhanced intracellular metabolic activity in virtually all cells of the body.
2. Once bound to the intranuclear receptors, the thyroid hormones can continue to express their control functions for days or even weeks.

Measurement of Hormone Concentrations in the Blood

Most hormones are present in the blood in extremely minute quantities; some concentrations are as low as one billionth of a milligram (1 picogram) per milliliter. Therefore, it was difficult to measure these concentrations by the usual chemical means. An extremely sensitive method, however, was developed about 45 years ago that revolutionized the measurement of hormones, their precursors, and their metabolic end products. This method is called *radioimmunoassay.*

Radioimmunoassay

The method of performing radioimmunoassay is as follows. First, an antibody that is highly specific for the hormone to be measured is produced.

Second, a small quantity of this antibody is (1) mixed with a quantity of fluid from the animal containing the hormone to be measured and (2) mixed simultaneously with an appropriate amount of purified standard hormone that has been tagged with a radioactive isotope. However, one specific condition must be met: There must be too little antibody to bind completely both the

radioactively tagged hormone and the hormone in the fluid to be assayed. Therefore, the natural hormone in the assay fluid and the radioactive standard hormone *compete for the binding sites* of the antibody. In the process of competing, the quantity of each of the two hormones, the natural and the radioactive, that binds is proportional to its concentration in the assay fluid.

Third, after binding has reached equilibrium, the antibody-hormone complex is separated from the remainder of the solution, and the quantity of radioactive hormone bound in this complex is measured by radioactive counting techniques. If a large amount of radioactive hormone has bound with the antibody, it is clear that there was only a small amount of natural hormone to compete with the radioactive hormone, and therefore the concentration of the natural hormone in the assayed fluid was small. Conversely, if only a small amount of radioactive hormone has bound, it is clear that there was a large amount of natural hormone to compete for the binding sites.

Fourth, to make the assay highly quantitative, the radioimmunoassay procedure is also performed for "standard" solutions of untagged hormone at several concentration levels. Then a "standard curve" is plotted, as shown in Figure 74-9. By comparing the radioactive counts recorded from the "unknown" assay procedures with the standard curve, one can determine within an error of 10 to 15 percent the concentration of the hormone in the "unknown" assayed fluid. As little as billionths or even trillionths of a gram of hormone can often be assayed in this way.

Enzyme-Linked Immunosorbent Assay

Enzyme-linked immunosorbent assays (ELISAs) can be used to measure almost any protein, including hormones. This test combines the specificity of antibodies with the sensitivity of simple enzyme assays. Figure 74-10 shows the basic elements of this method, which is often performed on plastic plates that each have 96 small wells. Each well is coated with an antibody (AB_1) that is specific for the hormone being assayed. Samples or standards are added to each of the wells, followed by a second antibody (AB_2) that is also specific for the hormone but binds to a different site of the hormone molecule. A third antibody (AB_3) that is added recognizes AB_2 and is coupled to an enzyme that converts a suitable substrate to a product that can be easily detected by colorimetric or fluorescent optical methods.

Because each molecule of enzyme catalyzes the formation of many thousands of product molecules, even small amounts of hormone molecules can be detected. In contrast to competitive radioimmunoassay methods, ELISA methods use excess antibodies so that all hormone molecules are captured in antibody-hormone complexes. Therefore, the amount of hormone present in the sample or in the standard is proportional to the amount of product formed.

The ELISA method has become widely used in clinical laboratories because (1) it does not employ radioactive isotopes, (2) much of the assay can be automated using 96-well plates, and (3) it has proved to be a cost-effective and accurate method for assessing hormone levels.

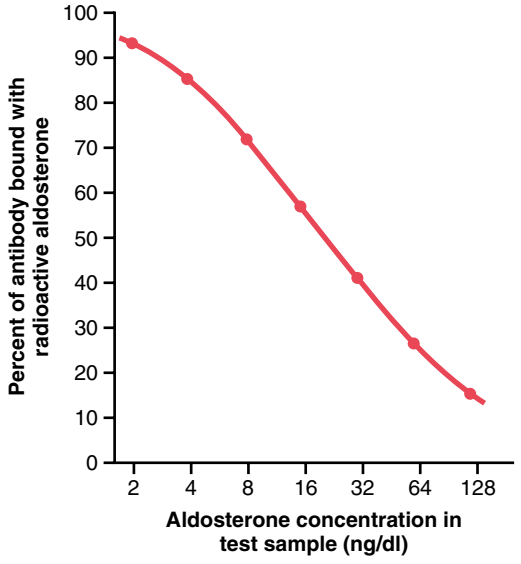


Figure 74-9 "Standard curve" for radioimmunoassay of aldosterone. (Courtesy Dr. Manis Smith.)

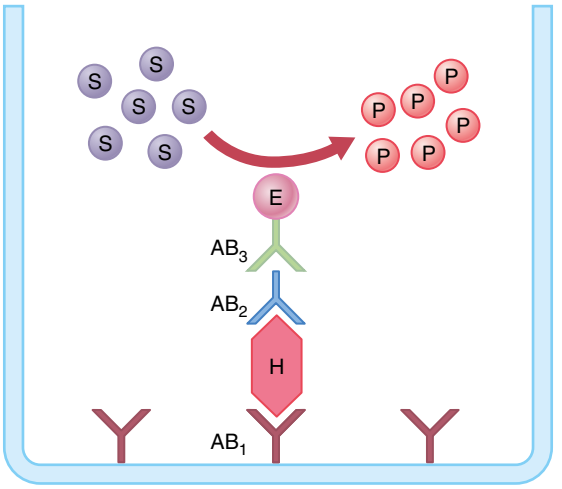


Figure 74-10 Basic principles of the enzyme-linked immunosorbent assay (ELISA) for measuring the concentration of a hormone (H). AB_1 and AB_2 are antibodies that recognize the hormone at different binding sites, and AB_3 is an antibody that recognizes AB_2. E is an enzyme linked to AB_3 that catalyzes the formation of a colored fluorescent product (P) from a substrate (S). The amount of the product is measured using optical methods and is proportional to the amount of hormone in the well if there are excess antibodies in the well.

Bibliography

Alberts B, Johnson A, Lewis J, et al: *Molecular Biology of the Cell*, ed 5, New York, 2008, Garland Science.

Antunes-Rodrigues J, de Castro M, Elias LL, et al: Neuroendocrine control of body fluid metabolism, *Physiol Rev* 84:169, 2004.

Aranda A, Pascual A: Nuclear hormone receptors and gene expression, *Physiol Rev* 81:1269, 2001.

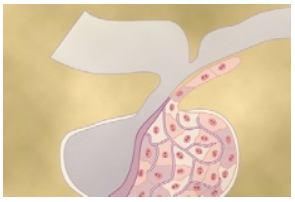
Bezbradica JS, Medzhitov R: Integration of cytokine and heterologous receptor signaling pathways, *Nat Immunol* 10:333, 2009.

Dayan CM, Panicker V: Novel insights into thyroid hormones from the study of common genetic variation, *Nat Rev Endocrinol* 5:211, 2009.

Funder JW: Reconsidering the roles of the mineralocorticoid receptor, *Hypertension* 53:286, 2009.
Gao Q, Horvath TL: Cross-talk between estrogen and leptin signaling in the hypothalamus, *Am J Physiol Endocrinol Metab* 294:E817, 2008.
Heldring N, Pike A, Andersson S, et al: Estrogen receptors: how do they signal and what are their targets? *Physiol Rev* 87:905, 2007.
Kuhn M: Structure, regulation, and function of mammalian membrane guanylyl cyclase receptors, with a focus on guanylyl cyclase-A, *Circ Res* 93:700, 2003.
Mogi M, Iwai M, Horiuchi M: Emerging concepts of regulation of angiotensin II receptors: new players and targets for traditional receptors, *Arterioscler Thromb Vasc Biol* 27:2532, 2007.
Morris AJ, Malbon CC: Physiological regulation of G protein-linked signaling, *Physiol Rev* 79:1373, 1999.
Pires-daSilva A, Sommer RJ: The evolution of signaling pathways in animal development, *Nat Rev Genet* 4:39, 2003.
Psarra AM, Sekeris CE: Glucocorticoid receptors and other nuclear transcription factors in mitochondria and possible functions, *Biochim Biophys Acta* 1787:431, 2009.
Spat A, Hunyady L: Control of aldosterone secretion: a model for convergence in cellular signaling pathways, *Physiol Rev* 84:489, 2004.
Tasken K, Aandahl EM: Localized effects of cAMP mediated by distinct routes of protein kinase A, *Physiol Rev* 84:137, 2004.
Wettschureck N, Offermanns S: Mammalian G proteins and their cell type specific functions, *Physiol Rev* 85:1159, 2005.
Yang J, Young MJ: The mineralocorticoid receptor and its coregulators, *J Mol Endocrinol* 43:53, 2009.
Yen PM: Physiological and molecular basis of thyroid hormone action, *Physiol Rev* 81:1097, 2001.

CHAPTER 75

Pituitary Hormones and Their Control by the Hypothalamus



Pituitary Gland and Its Relation to the Hypothalamus

The Pituitary Gland Has Two Distinct Parts—The Anterior and Posterior Lobes. The *pituitary gland* (Figure 75-1), also called the *hypophysis,* is a small gland—about 1 centimeter in diameter and 0.5 to 1 gram in weight—that lies in the *sella turcica,* a bony cavity at the base of the brain, and is connected to the hypothalamus by the *pituitary* (or *hypophysial*) stalk. Physiologically, the pituitary gland is divisible into two distinct portions: the *anterior pituitary,* also known as the *adenohypophysis,* and the *posterior pituitary,* also known as the *neurohypophysis.* Between these is a small, relatively avascular zone called the *pars intermedia,* which is much less developed in the human being but is larger and much more functional in some lower animals.

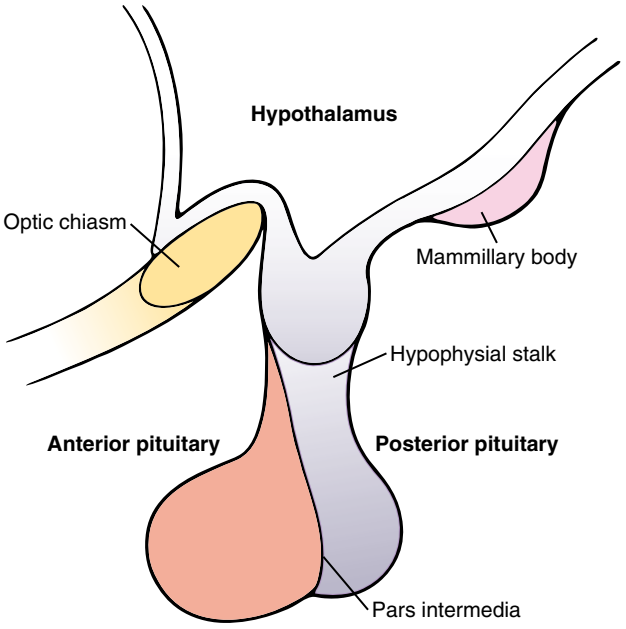


Figure 75-1 Pituitary gland.

Embryologically, the two portions of the pituitary originate from different sources—the anterior pituitary from *Rathke's pouch,* which is an embryonic invagination of the pharyngeal epithelium, and the posterior pituitary from a neural tissue outgrowth from the hypothalamus. The origin of the anterior pituitary from the pharyngeal epithelium explains the epithelioid nature of its cells, and the origin of the posterior pituitary from neural tissue explains the presence of large numbers of glial-type cells in this gland.

Six important peptide hormones plus several hormones of lesser importance are secreted by the *anterior* pituitary, and two important peptide hormones are secreted by the *posterior* pituitary. The hormones of the anterior pituitary play major roles in the control of metabolic functions throughout the body, as shown in Figure 75-2.

- *Growth hormone* promotes growth of the entire body by affecting protein formation, cell multiplication, and cell differentiation.

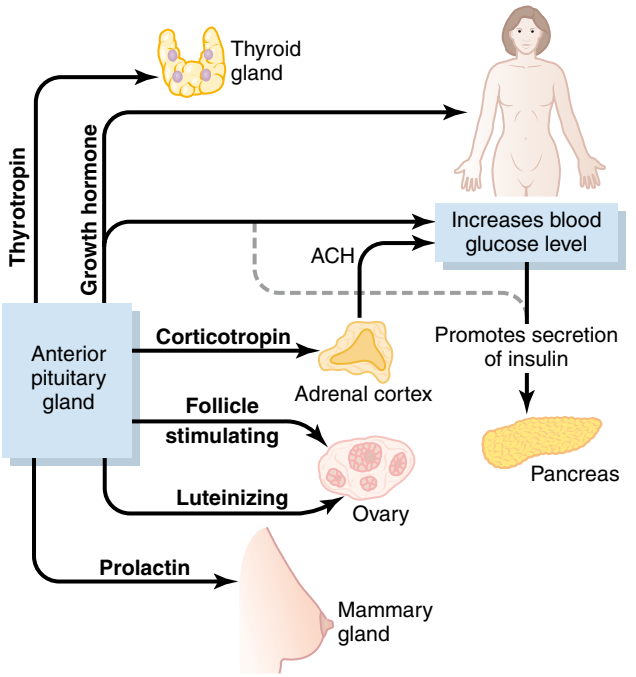


Figure 75-2 Metabolic functions of the anterior pituitary hormones. ACH, adrenal corticosteroid hormones.

- *Adrenocorticotropin (corticotropin)* controls the secretion of some of the adrenocortical hormones, which affect the metabolism of glucose, proteins, and fats.
- *Thyroid-stimulating hormone (thyrotropin)* controls the rate of secretion of thyroxine and triiodothyronine by the thyroid gland, and these hormones control the rates of most intracellular chemical reactions in the body.
- *Prolactin* promotes mammary gland development and milk production.
- Two separate gonadotropic hormones, *follicle-stimulating hormone* and *luteinizing hormone,* control growth of the ovaries and testes, as well as their hormonal and reproductive activities.

The two hormones secreted by the posterior pituitary play other roles.

- *Antidiuretic hormone* (also called *vasopressin*) controls the rate of water excretion into the urine, thus helping to control the concentration of water in the body fluids.
- *Oxytocin* helps express milk from the glands of the breast to the nipples during suckling and helps in the delivery of the baby at the end of gestation.

Anterior Pituitary Gland Contains Several Different Cell Types That Synthesize and Secrete Hormones. Usually, there is one cell type for each major hormone formed in the anterior pituitary gland. With special stains attached to high-affinity antibodies that bind with the distinctive hormones, at least five cell types can be differentiated (Figure 75-3). Table 75-1 provides a summary of these cell types, the hormones they produce, and their physiological actions. These five cell types are:

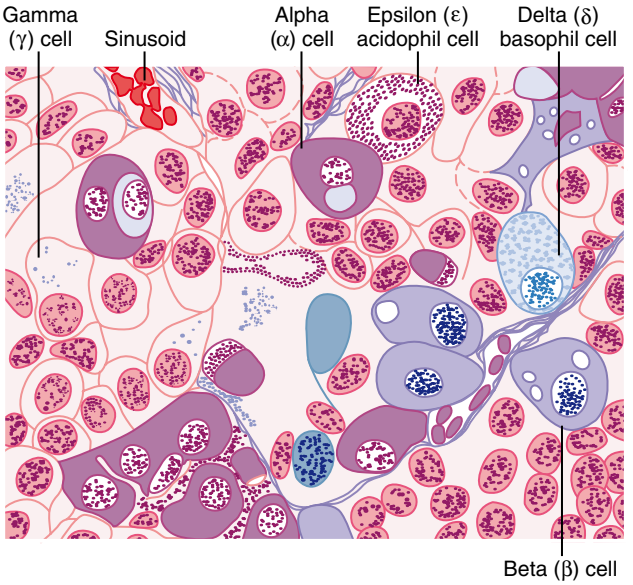


Figure 75-3 Cellular structure of the anterior pituitary gland. (Redrawn from Guyton AC: Physiology of the Human Body, 6th ed. Philadelphia: Saunders College Publishing, 1984.)

1. *Somatotropes*—human growth hormone (hGH)
2. *Corticotropes*—adrenocorticotropin (ACTH)
3. *Thyrotropes*—thyroid-stimulating hormone (TSH)
4. *Gonadotropes*—gonadotropic hormones, which include both luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
5. *Lactotropes*—prolactin (PRL)

Table 75-1 Cells and Hormones of the Anterior Pituitary Gland and Their Physiological Functions

Cell	Hormone	Chemistry	Physiological Action
Somatotropes	Growth hormone (GH; somatotropin)	Single chain of 191 amino acids	Stimulates body growth; stimulates secretion of IGF-1; stimulates lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism
Corticotropes	Adrenocorticotropic hormone (ACTH; corticotropin)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (TSH; thyrotropin)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids) Glycoprotein of two subunits, α (89 amino acids) and β (115 amino acids)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Lactotropes Mammotropes	Prolactin (PRL)	Single chain of 198 amino acids	Stimulates milk secretion and production

IGF, insulin-like growth factor.

About 30 to 40 percent of the anterior pituitary cells are somatotropes that secrete growth hormone, and about 20 percent are corticotropes that secrete ACTH. Each of the other cell types accounts for only 3 to 5 percent of the total; nevertheless, they secrete powerful hormones for controlling thyroid function, sexual functions, and milk secretion by the breasts.

Somatotropes stain strongly with acid dyes and are therefore called *acidophils.* Thus, pituitary tumors that secrete large quantities of human growth hormone are called *acidophilic tumors.*

Posterior Pituitary Hormones Are Synthesized by Cell Bodies in the Hypothalamus. The bodies of the cells that secrete the *posterior* pituitary hormones are not located in the pituitary gland itself but are large neurons, called *magnocellular neurons,* located in the *supraoptic* and *paraventricular nuclei* of the hypothalamus. The hormones are then transported in the axoplasm of the neurons' nerve fibers passing from the hypothalamus to the posterior pituitary gland. This is discussed later in the chapter.

Hypothalamus Controls Pituitary Secretion

Almost all secretion by the pituitary is controlled by either hormonal or nervous signals from the hypothalamus. Indeed, when the pituitary gland is removed from its normal position beneath the hypothalamus and transplanted to some other part of the body, its rates of secretion of the different hormones (except for prolactin) fall to very low levels.

Secretion from the posterior pituitary is controlled by nerve signals that originate in the hypothalamus and terminate in the posterior pituitary. In contrast, secretion by the anterior pituitary is controlled by hormones called *hypothalamic releasing* and *hypothalamic inhibitory hormones* (or *factors*) secreted within the hypothalamus and then conducted, as shown in Figure 75-4, to the anterior pituitary through minute blood vessels called *hypothalamic-hypophysial portal vessels.* In the anterior pituitary, these releasing and inhibitory hormones act on the glandular cells to control their secretion. This system of control is discussed in the next section of this chapter.

The hypothalamus receives signals from many sources in the nervous system. Thus, when a person is exposed to pain, a portion of the pain signal is transmitted into the hypothalamus. Likewise, when a person experiences some powerful depressing or exciting thought, a portion of the signal is transmitted into the hypothalamus. Olfactory stimuli denoting pleasant or unpleasant smells transmit strong signal components directly and through the amygdaloid nuclei into the hypothalamus. Even the concentrations of nutrients, electrolytes, water, and various hormones in the blood excite or inhibit various portions of the hypothalamus. Thus, the hypothalamus is a collecting center for information concerning the internal well-being of the body, and much of this information is used to control secretions of the many globally important pituitary hormones.

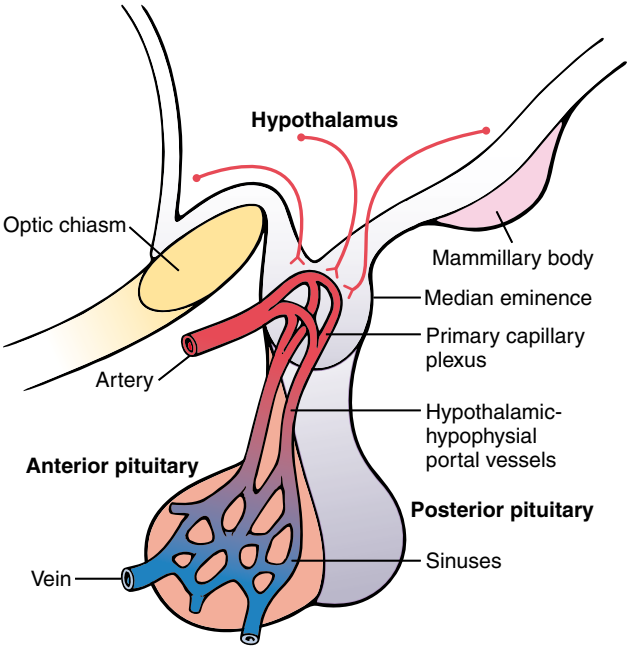


Figure 75-4 Hypothalamic-hypophysial portal system.

Hypothalamic-Hypophysial Portal Blood Vessels of the Anterior Pituitary Gland

The anterior pituitary is a highly vascular gland with extensive capillary sinuses among the glandular cells. Almost all the blood that enters these sinuses passes first through another capillary bed in the lower hypothalamus. The blood then flows through small *hypothalamic-hypophysial portal blood vessels* into the anterior pituitary sinuses. Figure 75-4 shows the lowermost portion of the hypothalamus, called the *median eminence,* which connects inferiorly with the pituitary stalk. Small arteries penetrate into the median eminence and then additional small vessels return to its surface, coalescing to form the hypothalamic-hypophysial portal blood vessels. These pass downward along the pituitary stalk to supply blood to the anterior pituitary sinuses.

Hypothalamic Releasing and Inhibitory Hormones Are Secreted into the Median Eminence. Special neurons in the hypothalamus synthesize and secrete the *hypothalamic releasing* and *inhibitory hormones* that control secretion of the anterior pituitary hormones. These neurons originate in various parts of the hypothalamus and send their nerve fibers to the median eminence and *tuber cinereum,* an extension of hypothalamic tissue into the pituitary stalk.

The endings of these fibers are different from most endings in the central nervous system, in that their function is not to transmit signals from one neuron to another but rather to secrete the hypothalamic releasing and inhibitory hormones into the tissue fluids. These hormones are

immediately absorbed into the hypothalamic-hypophysial portal system and carried directly to the sinuses of the anterior pituitary gland.

Hypothalamic Releasing and Inhibitory Hormones Control Anterior Pituitary Secretion. The function of the releasing and inhibitory hormones is to control secretion of the anterior pituitary hormones. For most of the anterior pituitary hormones, it is the releasing hormones that are important, but for prolactin, a hypothalamic inhibitory hormone probably exerts more control. The major hypothalamic releasing and inhibitory hormones are summarized in Table 75-2 and are the following:

1. *Thyrotropin-releasing hormone* (TRH), which causes release of thyroid-stimulating hormone
2. *Corticotropin-releasing hormone* (CRH), which causes release of adrenocorticotropin
3. *Growth hormone–releasing hormone* (GHRH), which causes release of growth hormone, and *growth hormone inhibitory hormone* (GHIH), also called *somatostatin,* which inhibits release of growth hormone
4. *Gonadotropin-releasing hormone* (GnRH), which causes release of the two gonadotropic hormones, luteinizing hormone and follicle-stimulating hormone
5. *Prolactin inhibitory hormone* (PIH), which causes inhibition of prolactin secretion

Additional hypothalamic hormones include one that stimulates prolactin secretion and perhaps others that inhibit release of the anterior pituitary hormones. Each of the more important hypothalamic hormones is discussed in detail as the specific hormonal systems controlled by them are presented in this and subsequent chapters.

Specific Areas in the Hypothalamus Control Secretion of Specific Hypothalamic Releasing and Inhibitory Hormones. All or most of the hypothalamic hormones are secreted at nerve endings in the median eminence before being transported to the anterior pituitary gland. Electrical stimulation of this region excites these nerve endings and, therefore, causes release of essentially all the hypothalamic hormones. However, the neuronal cell bodies that give rise to these median eminence nerve endings are located in other discrete areas of the hypothalamus or in closely related areas of the basal brain. The specific loci of the neuronal cell bodies that form the different hypothalamic releasing or inhibitory hormones are still poorly known, so it would be misleading to attempt delineation here.

Physiological Functions of Growth Hormone

All the major anterior pituitary hormones, except for growth hormone, exert their principal effects by stimulating target glands, including thyroid gland, adrenal cortex, ovaries, testicles, and mammary glands. The functions of each of these pituitary hormones are so intimately concerned with the functions of the respective target glands that, except for growth hormone, their functions are discussed in subsequent chapters along with the target glands. Growth hormone, in contrast to other hormones, does not function through a target gland but exerts its effects directly on all or almost all tissues of the body.

Growth Hormone Promotes Growth of Many Body Tissues

Growth hormone, also called *somatotropic hormone* or *somatotropin,* is a small protein molecule that contains 191 amino acids in a single chain and has a molecular weight of 22,005. It causes growth of almost all tissues of the body that are capable of growing. It promotes increased sizes of the cells and increased mitosis, with development of greater numbers of cells and specific differentiation of certain types of cells such as bone growth cells and early muscle cells.

Figure 75-5 shows typical weight charts of two growing littermate rats, one of which received daily injections of growth hormone and the other of which did not receive

Table 75-2 Hypothalamic Releasing and Inhibitory Hormones That Control Secretion of the Anterior Pituitary Gland

Hormone	Structure	Primary Action on Anterior Pituitary
Thyrotropin-releasing hormone (TRH)	Peptide of 3 amino acids	Stimulates secretion of TSH by thyrotropes
Gonadotropin-releasing hormone (GnRH)	Single chain of 10 amino acids	Stimulates secretion of FSH and LH by gonadotropes
Corticotropin-releasing hormone (CRH)	Single chain of 41 amino acids	Stimulates secretion of ACTH by corticotropes
Growth hormone-releasing hormone (GHRH)	Single chain of 44 amino acids	Stimulates secretion of growth hormone by somatotropes
Growth hormone inhibitory hormone (somatostatin)	Single chain of 14 amino acids	Inhibits secretion of growth hormone by somatotropes
Prolactin-inhibiting hormone (PIH)	Dopamine (a catecholamine)	Inhibits synthesis and secretion of prolactin by lactotropes

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

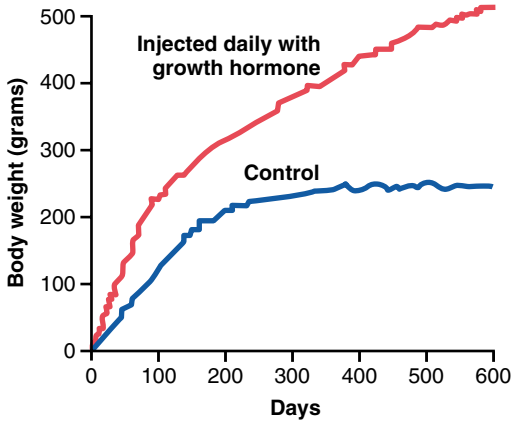


Figure 75-5 Comparison of weight gain of a rat injected daily with growth hormone with that of a normal littermate.

growth hormone. This figure shows marked enhancement of growth in the rat given growth hormone, in the early days of life and even after the two rats reached adulthood. In the early stages of development, all organs of the treated rat increased proportionately in size; after adulthood was reached, most of the bones stopped lengthening, but many of the soft tissues continued to grow. This results from the fact that once the epiphyses of the long bones have united with the shafts, further lengthening of bone cannot occur, even though most other tissues of the body can continue to grow throughout life.

Growth Hormone Has Several Metabolic Effects

Aside from its general effect in causing growth, growth hormone has multiple specific metabolic effects, including (1) increased rate of protein synthesis in most cells of the body; (2) increased mobilization of fatty acids from adipose tissue, increased free fatty acids in the blood, and increased use of fatty acids for energy; and (3) decreased rate of glucose utilization throughout the body. Thus, in effect, growth hormone enhances body protein, uses up fat stores, and conserves carbohydrates.

Growth Hormone Promotes Protein Deposition in Tissues

Although the precise mechanisms by which growth hormone increases protein deposition are not known, a series of different effects are known, all of which could lead to enhanced protein deposition.

Enhancement of Amino Acid Transport Through the Cell Membranes. Growth hormone directly enhances transport of most amino acids through the cell membranes to the interior of the cells. This increases the amino acid concentrations in the cells and is presumed to be at least partly responsible for the increased protein synthesis. This control of amino acid transport is similar to the effect of insulin in controlling glucose transport through the membrane, as discussed in Chapters 67 and 78.

Enhancement of RNA Translation to Cause Protein Synthesis by the Ribosomes. Even when the amino acid concentrations are not increased in the cells, growth hormone still increases RNA translation, causing protein to be synthesized in greater amounts by the ribosomes in the cytoplasm.

Increased Nuclear Transcription of DNA to Form RNA. Over more prolonged periods (24 to 48 hours), growth hormone also stimulates the transcription of DNA in the nucleus, causing the formation of increased quantities of RNA. This promotes more protein synthesis and promotes growth if sufficient energy, amino acids, vitamins, and other requisites for growth are available. In the long run, this may be the most important function of growth hormone.

Decreased Catabolism of Protein and Amino Acids. In addition to the increase in protein synthesis, there is a decrease in the breakdown of cell protein. A probable reason for this is that growth hormone also mobilizes large quantities of free fatty acids from the adipose tissue, and these are used to supply most of the energy for the body's cells, thus acting as a potent "protein sparer."

Summary. Growth hormone enhances almost all facets of amino acid uptake and protein synthesis by cells, while at the same time reducing the breakdown of proteins.

Growth Hormone Enhances Fat Utilization for Energy

Growth hormone has a specific effect in causing the release of fatty acids from adipose tissue and, therefore, increasing the concentration of fatty acids in the body fluids. In addition, in tissues throughout the body, growth hormone enhances the conversion of fatty acids to acetyl coenzyme A (acetyl-CoA) and its subsequent utilization for energy. Therefore, under the influence of growth hormone, fat is used for energy in preference to the use of carbohydrates and proteins.

Growth hormone's ability to promote fat utilization, together with its protein anabolic effect, causes an increase in lean body mass. However, mobilization of fat by growth hormone requires several hours to occur, whereas enhancement of protein synthesis can begin in minutes under the influence of growth hormone.

"Ketogenic" Effect of Excessive Growth Hormone. Under the influence of excessive amounts of growth hormone, fat mobilization from adipose tissue sometimes becomes so great that large quantities of acetoacetic acid are formed by the liver and released into the body fluids, thus causing *ketosis.* This excessive mobilization of fat from the adipose tissue also frequently causes a fatty liver.

Growth Hormone Decreases Carbohydrate Utilization

Growth hormone causes multiple effects that influence carbohydrate metabolism, including (1) decreased glucose uptake in tissues such as skeletal muscle and fat, (2) increased glucose production by the liver, and (3) increased insulin secretion.

Each of these changes results from growth hormone–induced "insulin resistance," which attenuates insulin's actions to stimulate the uptake and utilization of glucose in skeletal muscle and adipose tissue and to inhibit gluconeogenesis (glucose production) by the liver; this leads to increased blood glucose concentration and a compensatory increase in insulin secretion. For these reasons, growth hormone's effects are called *diabetogenic,* and excess secretion of growth hormone can produce metabolic disturbances similar to those found in patients with type II (non-insulin-dependent) diabetes, who are also resistant to the metabolic effects of insulin.

We do not know the precise mechanism by which growth hormone causes insulin resistance and decreased glucose utilization by the cells. However, growth hormone–induced increases in blood concentrations of fatty acids likely contribute to impairment of insulin's actions on tissue glucose utilization. Experimental studies indicate that raising blood levels of fatty acids above normal rapidly decreases the sensitivity of the liver and skeletal muscle to insulin's effects on carbohydrate metabolism.

Necessity of Insulin and Carbohydrate for the Growth-Promoting Action of Growth Hormone. Growth hormone fails to cause growth in animals that lack a pancreas; it also fails to cause growth if carbohydrates are excluded from the diet. This shows that adequate insulin activity and adequate availability of carbohydrates are necessary for growth hormone to be effective. Part of this requirement for carbohydrates and insulin is to provide the energy needed for the metabolism of growth, but there seem to be other effects as well. Especially important is insulin's ability to enhance the transport of some amino acids into cells, in the same way that it stimulates glucose transport.

Growth Hormone Stimulates Cartilage and Bone Growth

Although growth hormone stimulates increased deposition of protein and increased growth in almost all tissues of the body, its most obvious effect is to increase growth of the skeletal frame. This results from multiple effects of growth hormone on bone, including (1) increased deposition of protein by the chondrocytic and osteogenic cells that cause bone growth, (2) increased rate of reproduction of these cells, and (3) a specific effect of converting chondrocytes into osteogenic cells, thus causing deposition of new bone.

There are two principal mechanisms of bone growth. First, in response to growth hormone stimulation, the long bones grow in length at the epiphyseal cartilages, where the epiphyses at the ends of the bone are separated from the shaft. This growth first causes deposition of new cartilage, followed by its conversion into new bone, thus elongating the shaft and pushing the epiphyses farther and farther apart. At the same time, the epiphyseal cartilage itself is progressively used up, so by late adolescence, no additional epiphyseal cartilage remains to provide for further long bone growth. At this time, bony fusion occurs between the shaft and the epiphysis at each end, so no further lengthening of the long bone can occur.

Second, *osteoblasts* in the bone periosteum and in some bone cavities deposit new bone on the surfaces of older bone. Simultaneously, *osteoclasts* in the bone (discussed in detail in Chapter 79) remove old bone. When the rate of deposition is greater than that of resorption, the thickness of the bone increases. *Growth hormone strongly stimulates osteoblasts.* Therefore, the bones can continue to become thicker throughout life under the influence of growth hormone; this is especially true for the membranous bones. For instance, the jaw bones can be stimulated to grow even after adolescence, causing forward protrusion of the chin and lower teeth. Likewise, the bones of the skull can grow in thickness and give rise to bony protrusions over the eyes.

Growth Hormone Exerts Much of Its Effect Through Intermediate Substances Called "Somatomedins" (Also Called "Insulin-Like Growth Factors")

When growth hormone is supplied directly to cartilage chondrocytes cultured outside the body, proliferation or enlargement of the chondrocytes usually fails to occur. Yet growth hormone injected into the intact animal does cause proliferation and growth of the same cells.

In brief, it has been found that growth hormone causes the liver (and, to a much less extent, other tissues) to form several small proteins called *somatomedins* that have the potent effect of increasing all aspects of bone growth. Many of the somatomedin effects on growth are similar to the effects of insulin on growth. Therefore, the somatomedins are also called insulin-like growth factors (IGFs).

At least four somatomedins have been isolated, but by far the most important of these is *somatomedin C* (also called insulin-like growth factor-1, or IGF-I). The molecular weight of somatomedin C is about 7500, and its concentration in the plasma closely follows the rate of growth hormone secretion.

The pygmies of Africa have a congenital inability to synthesize significant amounts of somatomedin C. Therefore, even though their plasma concentration of growth hormone is either normal or high, they have diminished amounts of somatomedin C in the plasma; this apparently accounts for the small stature of these people. Some other dwarfs (e.g., the Lévi-Lorain dwarf) also have this problem.

It has been postulated that most, if not all, of the growth effects of growth hormone result from somatomedin C and other somatomedins, rather than from direct effects of growth hormone on the bones and other peripheral tissues. Even so, experiments have demonstrated that injection of growth hormone directly into the epiphyseal cartilages of bones of living animals causes the specific growth of these cartilage areas, and the amount of growth hormone required for this is minute. Some aspects of the somatomedin hypothesis are still questionable.

One possibility is that growth hormone can cause the formation of enough somatomedin C in the local tissue to cause local growth. It is also possible that growth hormone itself is directly responsible for increased growth in some tissues and that the somatomedin mechanism is an alternative means of increasing growth but not always a necessary one.

Short Duration of Action of Growth Hormone but Prolonged Action of Somatomedin C. Growth hormone attaches only weakly to the plasma proteins in the blood. Therefore, it is released from the blood into the tissues rapidly, having a half-time in the blood of less than 20 minutes. By contrast, somatomedin C attaches strongly to a carrier protein in the blood that, like somatomedin C, is produced in response to growth hormone. As a result, somatomedin C is released only slowly from the blood to the tissues, with a half-time of about 20 hours. This greatly prolongs the growth-promoting effects of the bursts of growth hormone secretion shown in Figure 75-6.

Regulation of Growth Hormone Secretion

For many years it was believed that growth hormone was secreted primarily during the period of growth but then disappeared from the blood at adolescence. This has proved to be untrue. After adolescence, secretion decreases slowly with aging, finally falling to about 25 percent of the adolescent level in very old age.

Growth hormone is secreted in a pulsatile pattern, increasing and decreasing. The precise mechanisms that control secretion of growth hormone are not fully understood, but several factors related to a person's state of nutrition or stress are known to stimulate secretion: (1) *starvation,* especially with severe *protein deficiency;* (2) *hypoglycemia* or *low concentration of fatty acids in the blood;* (3) *exercise;* (4) *excitement;* (5) *trauma;* and (6) *ghrelin,* a hormone secreted by the stomach before meals. Growth hormone also characteristically increases during the first 2 hours of *deep sleep,* as shown in Figure 75-6. Table 75-3 summarizes some of the factors that are known to influence growth hormone secretion.

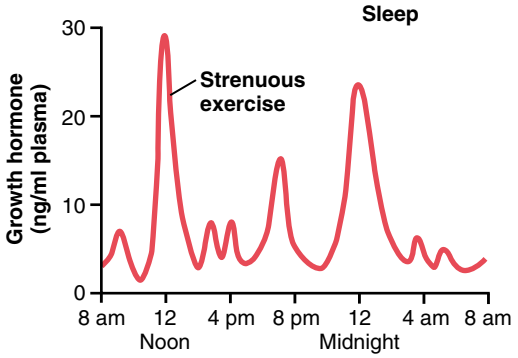


Figure 75-6 Typical variations in growth hormone secretion throughout the day, demonstrating the especially powerful effect of strenuous exercise and also the high rate of growth hormone secretion that occurs during the first few hours of deep sleep.

Table 75-3 Factors That Stimulate or Inhibit Secretion of Growth Hormone

Stimulate Growth Hormone Secretion	Inhibit Growth Hormone Secretion
Decreased blood glucose	Increased blood glucose
Decreased blood free fatty acids	Increased blood free fatty acids
Increased blood amino acids (arginine)	Aging
Starvation or fasting, protein deficiency	Obesity
Trauma, stress, excitement	Growth hormone inhibitory hormone (somatostatin)
Exercise	Growth hormone (exogenous)
Testosterone, estrogen	Somatomedins (insulin-like growth factors)
Deep sleep (stages II and IV)	
Growth hormone–releasing hormone	
Ghrelin	

The normal concentration of growth hormone in the plasma of an adult is between 1.6 and 3 ng/ml; in a child or adolescent, it is about 6 ng/ml. These values often increase to as high as 50 ng/ml after depletion of the body stores of proteins or carbohydrates during prolonged starvation.

Under acute conditions, hypoglycemia is a far more potent stimulator of growth hormone secretion than is an acute decrease in protein intake. Conversely, in chronic conditions, growth hormone secretion seems to correlate more with the degree of cellular protein depletion than with the degree of glucose insufficiency. For instance, the extremely high levels of growth hormone that occur during starvation are closely related to the amount of protein depletion.

Figure 75-7 demonstrates the effect of protein deficiency on plasma growth hormone and then the effect of adding protein to the diet. The first column shows very high levels of growth hormone in children with extreme protein deficiency during the protein malnutrition condition called *kwashiorkor;* the second column shows the levels in the same children after 3 days of treatment with more than adequate quantities of carbohydrates in their diets, demonstrating that the carbohydrates did not lower the plasma growth hormone concentration. The third and fourth columns show the levels after treatment with protein supplements for 3 and 25 days, respectively, with a concomitant decrease in the hormone.

These results demonstrate that under severe conditions of protein malnutrition, adequate calories alone are not sufficient to correct the excess production of growth hormone. The protein deficiency must also be corrected before the growth hormone concentration will return to normal.

Role of the Hypothalamus, Growth Hormone-Releasing Hormone, and Somatostatin in the Control of Growth Hormone Secretion

From the preceding description of the many factors that can affect growth hormone secretion, one can readily understand the perplexity of physiologists as they attempted

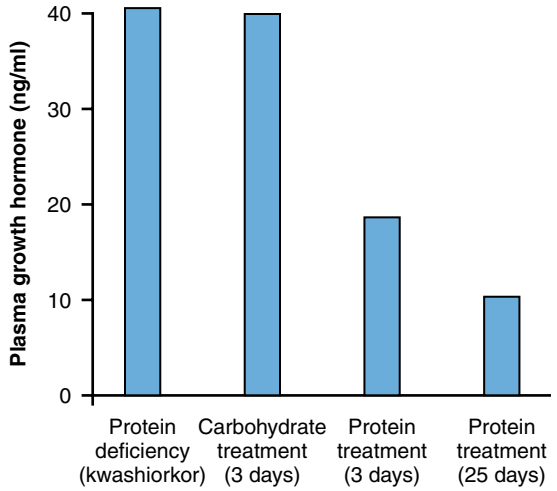


Figure 75-7 Effect of extreme protein deficiency on the plasma concentration of growth hormone in the disease kwashiorkor. Also shown is the failure of carbohydrate treatment but the effectiveness of protein treatment in lowering growth hormone concentration. (Drawn from data in Pimstone BL, Barbezat G, Hansen JD, et al: Studies on growth hormone secretion in protein-calorie malnutrition. Am J Clin Nutr 21:482, 1968.)

to unravel the mysteries of regulation of growth hormone secretion. It is known that growth hormone secretion is controlled by two factors secreted in the hypothalamus and then transported to the anterior pituitary gland through the hypothalamic-hypophysial portal vessels. They are *growth hormone–releasing hormone* and *growth hormone inhibitory hormone* (also called *somatostatin*). Both of these are polypeptides; GHRH is composed of 44 amino acids, and somatostatin is composed of 14 amino acids.

The part of the hypothalamus that causes secretion of GHRH is the ventromedial nucleus; this is the same area of the hypothalamus that is sensitive to blood glucose concentration, causing satiety in hyperglycemic states and hunger in hypoglycemic states. The secretion of somatostatin is controlled by other nearby areas of the hypothalamus. Therefore, it is reasonable to believe that some of the same signals that modify a person's behavioral feeding instincts also alter the rate of growth hormone secretion.

In a similar manner, hypothalamic signals depicting emotions, stress, and trauma can all affect hypothalamic control of growth hormone secretion. In fact, experiments have shown that catecholamines, dopamine, and serotonin, each of which is released by a different neuronal system in the hypothalamus, all increase the rate of growth hormone secretion.

Most of the control of growth hormone secretion is probably mediated through GHRH rather than through the inhibitory hormone somatostatin. GHRH stimulates growth hormone secretion by attaching to specific cell membrane receptors on the outer surfaces of the growth hormone cells in the pituitary gland. The receptors activate the adenylyl cyclase system inside the cell membrane, increasing the intracellular level of cyclic adenosine monophosphate (cAMP). This has both short-term and long-term effects. The short-term effect is to increase calcium ion transport into the cell; within minutes, this causes fusion of the growth hormone secretory vesicles with the cell membrane and release of the hormone into the blood. The long-term effect is to increase transcription in the nucleus by the genes to stimulate the synthesis of new growth hormone.

When growth hormone is administered directly into the blood of an animal over a period of hours, the rate of endogenous growth hormone secretion decreases. This demonstrates that growth hormone secretion is subject to typical negative feedback control, as is true for essentially all hormones. The nature of this feedback mechanism and whether it is mediated mainly through inhibition of GHRH or enhancement of somatostatin, which inhibits growth hormone secretion, are uncertain.

In summary, our knowledge of the regulation of growth hormone secretion is not sufficient to describe a composite picture. Yet because of the extreme secretion of growth hormone during starvation and its important long-term effect to promote protein synthesis and tissue growth, we can propose the following: the major long-term controller of growth hormone secretion is the long-term state of nutrition of the tissues themselves, especially their level of protein nutrition. That is, nutritional deficiency or excess tissue need for cellular proteins—for instance, after a severe bout of exercise when the muscles' nutritional status has been taxed—in some way increases the rate of growth hormone secretion. Growth hormone, in turn, promotes synthesis of new proteins while at the same time conserving the proteins already present in the cells.

Abnormalities of Growth Hormone Secretion

Panhypopituitarism. This term means decreased secretion of all the anterior pituitary hormones. The decrease in secretion may be congenital (present from birth), or it may occur suddenly or slowly at any time during life, most often resulting from a pituitary tumor that destroys the pituitary gland.

Dwarfism. Most instances of dwarfism result from generalized deficiency of anterior pituitary secretion (panhypopituitarism) during childhood. In general, all the physical parts of the body develop in appropriate proportion to one another, but the rate of development is greatly decreased. A child who has reached the age of 10 years may have the bodily development of a child aged 4 to 5 years, and the same person at age 20 years may have the bodily development of a child aged 7 to 10 years.

A person with panhypopituitary dwarfism does not pass through puberty and never secretes sufficient quantities of gonadotropic hormones to develop adult sexual functions. In one third of such dwarfs, however, only growth hormone is deficient; these persons do mature sexually and occasionally reproduce. In one type of dwarfism (the African pygmy and the Lévi-Lorain dwarf), the rate of growth hormone secretion is normal or high, but there is a hereditary inability to form somatomedin C, which is a key step for the promotion of growth by growth hormone.

Treatment with Human Growth Hormone. Growth hormones from different species of animals are sufficiently

different from one another that they will cause growth only in the one species or, at most, closely related species. For this reason, growth hormone prepared from lower animals (except, to some extent, from primates) is not effective in human beings. Therefore, the growth hormone of the human being is called *human growth hormone* to distinguish it from the others.

In the past, because growth hormone had to be prepared from human pituitary glands, it was difficult to obtain sufficient quantities to treat patients with growth hormone deficiency, except on an experimental basis. However, human growth hormone can now be synthesized by *Escherichia coli* bacteria as a result of successful application of recombinant DNA technology. Therefore, this hormone is now available in sufficient quantities for treatment purposes. Dwarfs who have pure growth hormone deficiency can be completely cured if treated early in life. Human growth hormone may also prove to be beneficial in other metabolic disorders because of its widespread metabolic functions.

Panhypopituitarism in the Adult. Panhypopituitarism first occurring in adulthood frequently results from one of three common abnormalities. Two tumorous conditions, craniopharyngiomas or chromophobe tumors, may compress the pituitary gland until the functioning anterior pituitary cells are totally or almost totally destroyed. The third cause is thrombosis of the pituitary blood vessels. This abnormality occasionally occurs when a new mother develops circulatory shock after the birth of her baby.

The general effects of adult panhypopituitarism are (1) hypothyroidism, (2) depressed production of glucocorticoids by the adrenal glands, and (3) suppressed secretion of the gonadotropic hormones so that sexual functions are lost. Thus, the picture is that of a lethargic person (from lack of thyroid hormones) who is gaining weight (because of lack of fat mobilization by growth, adrenocorticotropic, adrenocortical, and thyroid hormones) and has lost all sexual functions. Except for the abnormal sexual functions, the patient can usually be treated satisfactorily by administering adrenocortical and thyroid hormones.

Gigantism. Occasionally, the acidophilic, growth hormone–producing cells of the anterior pituitary gland become excessively active, and sometimes even acidophilic tumors occur in the gland. As a result, large quantities of growth hormone are produced. All body tissues grow rapidly, including the bones. If the condition occurs before adolescence, before the epiphyses of the long bones have become fused with the shafts, height increases so that the person becomes a giant—up to 8 feet tall.

The giant ordinarily has *hyperglycemia,* and the beta cells of the islets of Langerhans in the pancreas are prone to degenerate because they become overactive owing to the hyperglycemia. Consequently, in about 10 percent of giants, full-blown *diabetes mellitus* eventually develops.

In most giants, panhypopituitarism eventually develops if they remain untreated because the gigantism is usually caused by a tumor of the pituitary gland that grows until the gland itself is destroyed. This eventual general deficiency of pituitary hormones usually causes death in early adulthood. However, once gigantism is diagnosed, further effects can often be blocked by microsurgical removal of the tumor or by irradiation of the pituitary gland.

Acromegaly. If an acidophilic tumor occurs after adolescence—that is, after the epiphyses of the long bones have fused with the shafts—the person cannot grow taller, but the bones can become thicker and the soft tissues can continue to grow. This condition, shown in Figure 75-8, is known as *acromegaly.* Enlargement is especially marked in the bones of the hands and feet and in the *membranous bones,* including the cranium, nose, bosses on the forehead, supraorbital ridges, lower jawbone, and portions of the vertebrae, because their growth does not cease at adolescence. Consequently, the lower jaw protrudes forward, sometimes as much as half an inch, the forehead slants forward because of excess development of the supraorbital ridges, the nose increases to as much as twice normal size, the feet require size 14 or larger shoes, and the fingers become extremely thickened so that the hands are almost twice normal size. In addition to these effects, changes in the vertebrae ordinarily cause a hunched

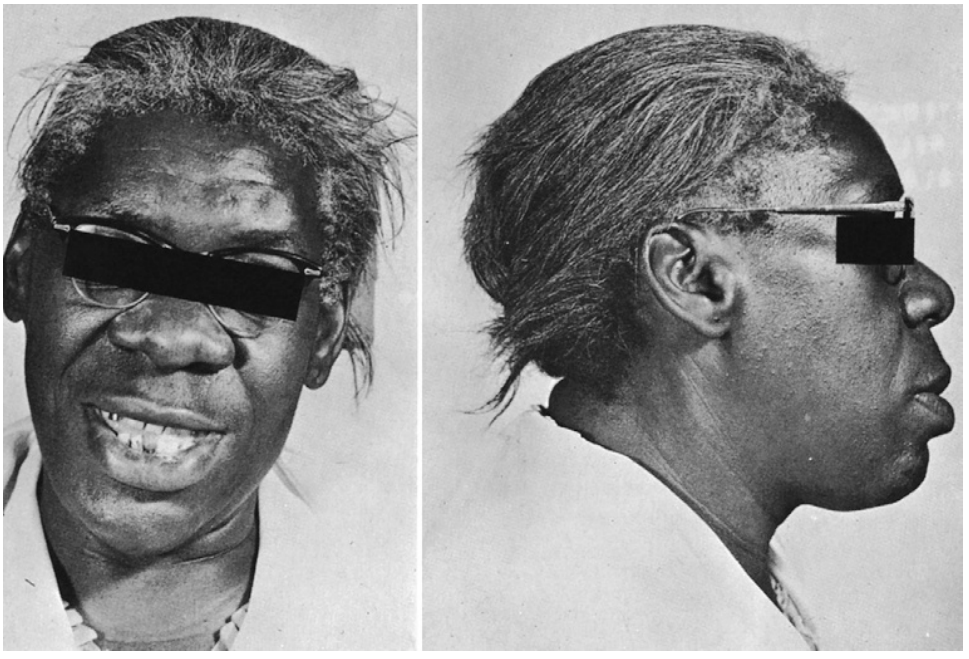


Figure 75-8 Acromegalic patient

back, which is known clinically as *kyphosis.* Finally, many soft tissue organs, such as the tongue, the liver, and especially the kidneys, become greatly enlarged.

Possible Role of Decreased Growth Hormone Secretion in Causing Changes Associated with Aging

In people who have lost the ability to secrete growth hormone, some features of the aging process accelerate. For instance, a 50-year-old person who has been without growth hormone for many years may have the appearance of a person aged 65. The aged appearance seems to result mainly from decreased protein deposition in most tissues of the body and increased fat deposition in its place. The physical and physiological effects are increased wrinkling of the skin, diminished rates of function of some of the organs, and diminished muscle mass and strength.

As one ages, the average plasma concentration of growth hormone in an otherwise normal person changes approximately as follows:

	ng/ml
5 to 20 years	6
20 to 40 years	3
40 to 70 years	1.6

Thus, it is possible that some of the normal aging effects result from diminished growth hormone secretion. In fact, some studies of growth hormone therapy in older people have demonstrated three important beneficial effects: (1) increased protein deposition in the body, especially in the muscles; (2) decreased fat deposits; and (3) a feeling of increased energy. Other studies, however, have shown that treatment of elderly patients with recombinant growth hormone may produce several undesirable side effects including insulin resistance and diabetes, edema, carpal tunnel syndrome, and arthralgias (joint pain). Therefore, recombinant growth hormone therapy is generally not recommended for use in healthy elderly patients with normal endocrine function.

Posterior Pituitary Gland and Its Relation to the Hypothalamus

The *posterior pituitary gland,* also called the *neurohypophysis,* is composed mainly of glial-like cells called *pituicytes.* The pituicytes do not secrete hormones; they act simply as a supporting structure for large numbers of *terminal nerve fibers* and *terminal nerve endings* from nerve tracts that originate in the *supraoptic* and *paraventricular nuclei* of the hypothalamus, as shown in Figure 75-9. These tracts pass to the neurohypophysis through the *pituitary stalk* (hypophysial stalk). The nerve endings are bulbous knobs that contain many secretory granules. These endings lie on the surfaces of capillaries, where they secrete two posterior pituitary hormones: (1) *antidiuretic hormone* (ADH), also called *vasopressin,* and (2) *oxytocin.*

If the pituitary stalk is cut above the pituitary gland but the entire hypothalamus is left intact, the posterior pituitary hormones continue to be secreted normally, after a transient decrease for a few days; they are then secreted by the cut ends of the fibers within the hypothalamus and not by the

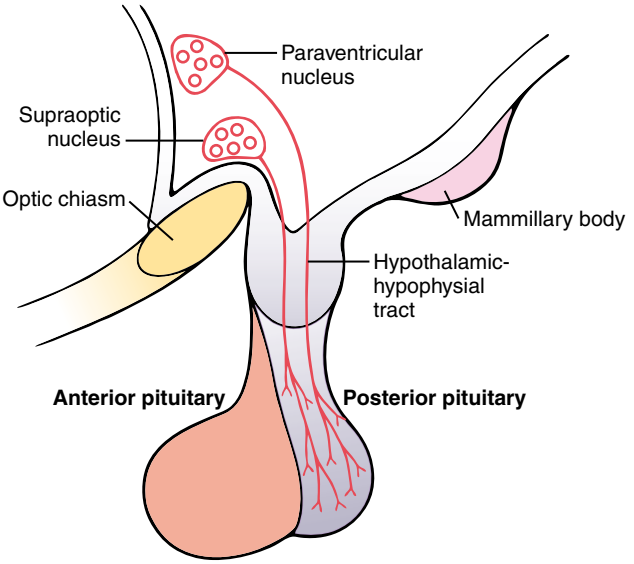


Figure 75-9 Hypothalamic control of the posterior pituitary.

nerve endings in the posterior pituitary. The reason for this is that the hormones are initially synthesized in the cell bodies of the supraoptic and paraventricular nuclei and are then transported in combination with "carrier" proteins called *neurophysins* down to the nerve endings in the posterior pituitary gland, requiring several days to reach the gland.

ADH is formed primarily in the supraoptic nuclei, whereas oxytocin is formed primarily in the paraventricular nuclei. Each of these nuclei can synthesize about one sixth as much of the second hormone as of its primary hormone.

When nerve impulses are transmitted downward along the fibers from the supraoptic or paraventricular nuclei, the hormone is immediately released from the secretory granules in the nerve endings by the usual secretory mechanism of *exocytosis* and is absorbed into adjacent capillaries. Both the neurophysin and the hormone are secreted together, but because they are only loosely bound to each other, the hormone separates almost immediately. The neurophysin has no known function after leaving the nerve terminals.

Chemical Structures of Antidiuretic Hormone and Oxytocin

Both oxytocin and ADH (vasopressin) are polypeptides, each containing nine amino acids. Their amino acid sequences are the following:

Vasopressin: Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-GlyNH_2
Oxytocin: Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-GlyNH_2

Note that these two hormones are almost identical except that in vasopressin, phenylalanine and arginine replace isoleucine and leucine of the oxytocin molecule. The similarity of the molecules explains their partial functional similarities.

Physiological Functions of Antidiuretic Hormone

The injection of extremely minute quantities of ADH—as small as 2 nanograms—can cause decreased excretion of water by the kidneys (antidiuresis). This antidiuretic effect is discussed in detail in Chapter 28. Briefly, in the absence of ADH, the collecting tubules and ducts become almost impermeable to water, which prevents significant reabsorption of water and therefore allows extreme loss

of water into the urine, also causing extreme dilution of the urine. Conversely, in the presence of ADH, the permeability of the collecting ducts and tubules to water increases greatly and allows most of the water to be reabsorbed as the tubular fluid passes through these ducts, thereby conserving water in the body and producing very concentrated urine.

The precise mechanism by which ADH acts on the collecting ducts to increase their permeability is only partially known. Without ADH, the luminal membranes of the tubular epithelial cells of the collecting ducts are almost impermeable to water. However, immediately inside the cell membrane are a large number of special vesicles that have highly water-permeable pores called *aquaporins.* When ADH acts on the cell, it first combines with membrane receptors that activate adenylyl cyclase and cause the formation of cAMP inside the tubular cell cytoplasm. This causes phosphorylation of elements in the special vesicles, which then causes the vesicles to insert into the apical cell membranes, thus providing many areas of high water permeability. All this occurs within 5 to 10 minutes. Then, in the absence of ADH, the entire process reverses in another 5 to 10 minutes. Thus, this process temporarily provides many new pores that allow free diffusion of water from the tubular fluid through the tubular epithelial cells and into the renal interstitial fluid. Water is then absorbed from the collecting tubules and ducts by osmosis, as explained in Chapter 28 in relation to the urine-concentrating mechanism of the kidneys.

Regulation of Antidiuretic Hormone Production

Increased Extracellular Fluid Osmolarity Stimulates Antidiuretic Hormone Secretion. When a concentrated electrolyte solution is injected into the artery that supplies the hypothalamus, the ADH neurons in the supraoptic and paraventricular nuclei immediately transmit impulses into the posterior pituitary to release large quantities of ADH into the circulating blood, sometimes increasing the ADH secretion to as high as 20 times normal. Conversely, injection of a dilute solution into this artery causes cessation of the impulses and therefore almost total cessation of ADH secretion. Thus, the concentration of ADH in the body fluids can change from small amounts to large amounts, or vice versa, in only a few minutes.

Somewhere in or near the hypothalamus are modified neuron receptors called *osmoreceptors.* When the extracellular fluid becomes too concentrated, fluid is pulled by osmosis out of the osmoreceptor cell, decreasing its size and initiating appropriate nerve signals in the hypothalamus to cause additional ADH secretion. Conversely, when the extracellular fluid becomes too dilute, water moves by osmosis in the opposite direction, into the cell, and this decreases the signal for ADH secretion. Although some researchers place these osmoreceptors in the hypothalamus itself (possibly even in the supraoptic nuclei), others believe that they are located in the *organum vasculosum,* a highly vascular structure in the anteroventral wall of the third ventricle.

Regardless of the mechanism, concentrated body fluids stimulate the supraoptic nuclei, whereas dilute body fluids inhibit them. A feedback control system is available to control the total osmotic pressure of the body fluids.

Further details on the control of ADH secretion and the role of ADH in controlling renal function and body fluid osmolality are presented in Chapter 28.

Low Blood Volume and Low Blood Pressure Stimulate ADH Secretion—Vasoconstrictor Effects of ADH

Whereas minute concentrations of ADH cause increased water conservation by the kidneys, higher concentrations of ADH have a potent effect of constricting the arterioles throughout the body and therefore increasing the arterial pressure. For this reason, ADH has another name, *vasopressin.*

One of the stimuli for causing intense ADH secretion is decreased blood volume. This occurs strongly when the blood volume decreases 15 to 25 percent or more; the secretory rate then sometimes rises to as high as 50 times normal. The cause of this is the following.

The atria have stretch receptors that are excited by overfilling. When excited, they send signals to the brain to inhibit ADH secretion. Conversely, when the receptors are unexcited as a result of underfilling, the opposite occurs, with greatly increased ADH secretion. Decreased stretch of the baroreceptors of the carotid, aortic, and pulmonary regions also stimulates ADH secretion. For further details about this blood volume-pressure feedback mechanism, refer to Chapter 28.

Oxytocic Hormone

Oxytocin Causes Contraction of the Pregnant Uterus. The hormone *oxytocin,* in accordance with its name, powerfully stimulates contraction of the pregnant uterus, especially toward the end of gestation. Therefore, many obstetricians believe that this hormone is at least partially responsible for causing birth of the baby. This is supported by the following facts: (1) In a hypophysectomized animal, the duration of labor is prolonged, indicating a possible effect of oxytocin during delivery. (2) The amount of oxytocin in the plasma increases during labor, especially during the last stage. (3) Stimulation of the cervix in a pregnant animal elicits nervous signals that pass to the hypothalamus and cause increased secretion of oxytocin. These effects and this possible mechanism for aiding in the birth process are discussed in more detail in Chapter 82.

Oxytocin Aids in Milk Ejection by the Breasts. Oxytocin also plays an especially important role in lactation—a role that is far better understood than its role in delivery. In lactation, oxytocin causes milk to be expressed from the alveoli into the ducts of the breast so that the baby can obtain it by suckling.

This mechanism works as follows: The suckling stimulus on the nipple of the breast causes signals to be transmitted through sensory nerves to the oxytocin neurons in the paraventricular and supraoptic nuclei in the hypothalamus, which causes release of oxytocin by the posterior pituitary gland. The oxytocin is then carried by the blood to the breasts, where it causes contraction of *myoepithelial cells* that lie outside of and form a latticework surrounding the alveoli of the mammary glands. In less than a minute after the beginning of suckling, milk begins to flow. This mechanism is called *milk letdown* or *milk ejection.* It is discussed further in Chapter 82 in relation to the physiology of lactation.

Bibliography

Antunes-Rodrigues J, de Castro M, Elias LL, et al: Neuroendocrine control of body fluid metabolism, *Physiol Rev* 84:169, 2004.

Boone M, Deen PM: Physiology and pathophysiology of the vasopressin-regulated renal water reabsorption, *Pflugers Arch* 456:1005, 2008.

Burbach JP, Luckman SM, Murphy D, et al: Gene regulation in the magnocellular hypothalamo-neurohypophysial system, *Physiol Rev* 81:1197, 2001.

Chiamolera MI, Wondisford FE: Thyrotropin-releasing hormone and the thyroid hormone feedback mechanism, *Endocrinology* 150:1091, 2009.

Dattani M, Preece M: Growth hormone deficiency and related disorders: insights into causation, diagnosis, and treatment, *Lancet* 363:1977, 2004.

Donaldson ZR, Young LJ: Oxytocin, vasopressin, and the neurogenetics of sociality, *Science* 322:900, 2008.

Dunger DB: Determinants of short stature and the response to growth hormone therapy, *Horm Res* 71(Suppl 2):2, 2009.

Eugster EA, Pescovitz OH: Gigantism, *J Clin Endocrinol Metab* 84:4379, 1999.

Freeman ME, Kanyicska B, Lerant A, et al: Prolactin: structure, function, and regulation of secretion, *Physiol Rev* 80:1523, 2000.

Gimpl G, Fahrenholz F: The oxytocin receptor system: structure, function, and regulation, *Physiol Rev* 81:629, 2001.

Lohmeier TE: Neurohypophysial hormones, *Am J Physiol Regul Integr Comp Physiol* 285:R715, 2003.

McEwen BS: Physiology and neurobiology of stress and adaptation: central role of the brain, *Physiol Rev* 87:873, 2007.

Melmed S: Acromegaly pathogenesis and treatment, *J Clin Invest* 119:3189, 2009.

Møller N, Jørgensen JO: Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects, *Endocr Rev* 30:152, 2009.

Nielsen S, Frokiaer J, Marples D, et al: Aquaporins in the kidney: from molecules to medicine, *Physiol Rev* 82:205, 2002.

Ohlsson C, Mohan S, Sjögren K, et al: The role of liver-derived insulin-like growth factor-I, *Endocr Rev* 30:494, 2009.

Rosenfeld RG: The future of research into growth hormone responsiveness, *Horm Res* 71(Suppl 2):71, 2009.

Rosenfeld RG, Hwa V: The growth hormone cascade and its role in mammalian growth, *Horm Res* 71(Suppl 2):36, 2009.

Schrier RW: Vasopressin and aquaporin 2 in clinical disorders of water homeostasis, *Semin Nephrol* 28:289, 2008.

Stricker EM, Sved AF: Controls of vasopressin secretion and thirst: similarities and dissimilarities in signals, *Physiol Behav* 77:731, 2002.

Zhu X, Gleiberman AS, Rosenfeld MG: Molecular physiology of pituitary development: signaling and transcriptional networks, *Physiol Rev* 87:933, 2007.