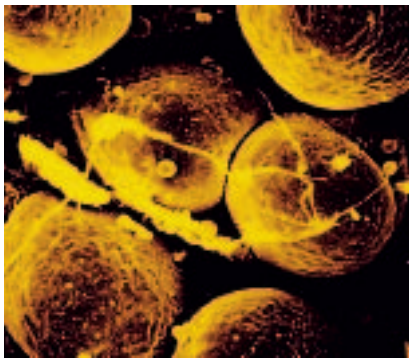


chapter 23

HORMONAL REGULATION AND INTEGRATION OF MAMMALIAN METABOLISM

We recognize that each tissue and, more generally, each cell of the organism secretes . . . special products or ferments into the blood which thereby influence all the other cells thus integrated with each other by a mechanism other than the nervous system.

—*Charles Édouard Brown-Séquard and J. d'Arsonval, article in* Comptes Rendus de la Société de Biologie, *1891*

In Chapters 13 through 22 we have discussed metabolism at the level of the individual cell, emphasizing central pathways common to almost all cells, prokaryotic and eukaryotic. We have seen how metabolic processes within cells are regulated at the level of individual enzyme reactions, by substrate availability, by allosteric mechanisms, and by phosphorylation or other covalent modifications of enzymes.

To appreciate fully the significance of individual metabolic pathways and their regulation, we must view these pathways in the context of the whole organism. An essential characteristic of multicellular organisms is cell differentiation and division of labor. The specialized functions of the tissues and organs of complex organisms such as humans impose characteristic fuel requirements and patterns of metabolism. Hormonal signals integrate and coordinate the metabolic activities of different tissues and optimize the allocation of fuels and precursors to each organ.

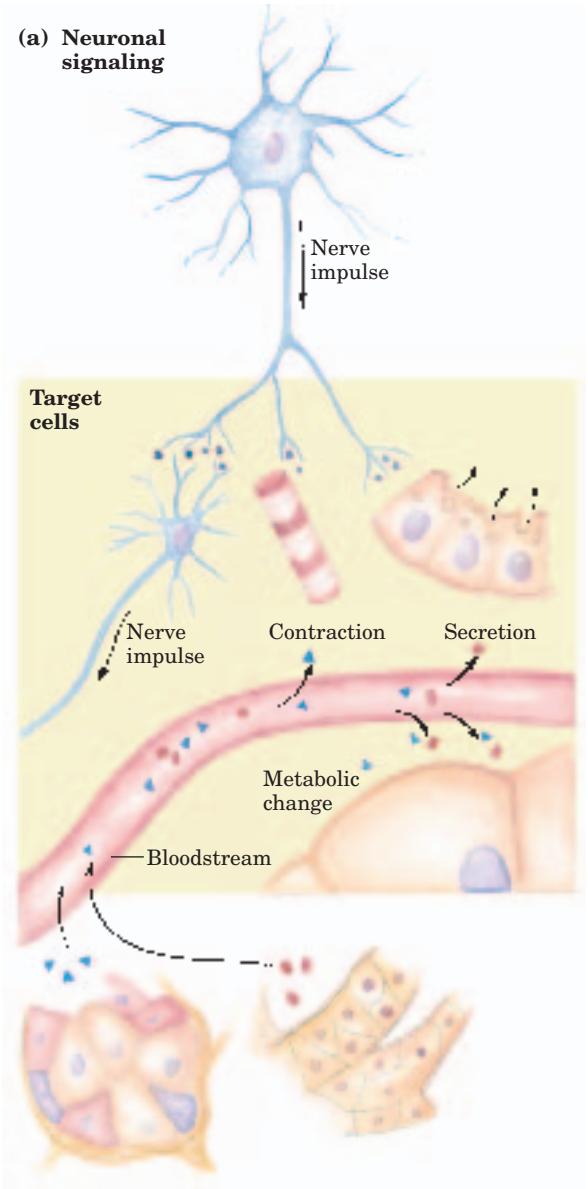
In this chapter we focus on mammals, looking at the specialized metabolism of several major organs and tissues and the integration of metabolism in the whole organism. We begin by examining the broad range of hormones and hormonal mechanisms, then turn to the tissue-specific functions regulated by these mechanisms. We discuss the distribution of nutrients to various organs—emphasizing the central role played by the liver—and the metabolic cooperation among these organs. To illustrate the integrative role of hormones, we describe the interplay of insulin, glucagon, and epinephrine in coordinating fuel metabolism in muscle, liver, and adipose tissue. The metabolic disturbances in diabetes further illustrate the importance of hormonal regulation of metabolism. Finally we discuss the long-term hormonal regulation of body mass.

23.1 Hormones: Diverse Structures for Diverse Functions

Virtually every process in a complex organism is regulated by one or more hormones: maintenance of blood pressure, blood volume, and electrolyte balance; embryogenesis; sexual differentiation, development, and reproduction; hunger, eating behavior, digestion, and

fuel allocation—to name but a few. We examine here the methods for detecting and measuring hormones and their interaction with receptors, and consider a representative selection of hormone types.

The coordination of metabolism in mammals is achieved by the **neuroendocrine system.** Individual cells in one tissue sense a change in the organism's circumstances and respond by secreting a chemical messenger that passes to another cell in the same or different tissue, where it binds to a receptor molecule and triggers a change in this second cell. In neuronal signaling (Fig. 23–1a), the chemical messenger (neurotransmitter; acetylcholine, for example) may travel only a fraction of a micrometer, across the synaptic cleft to the next neuron in a network. In hormonal signaling, the messengers—hormones—are carried in the bloodstream to neighboring cells or to distant organs and tissues; they may travel a meter or more before encountering their target cell (Fig. 23–1b). Except for this anatomic difference, these two chemical signaling mechanisms are remarkably similar. Epinephrine and norepinephrine, for example, serve as neurotransmitters in certain synapses of the brain and smooth muscle and as hormones that regulate fuel metabolism in liver and muscle. The following discussion of cellular signaling emphasizes hormone action, drawing on discussions of fuel metabolism in earlier chapters, but most of the fundamental mechanisms described here also occur in neurotransmitter action.



The Discovery and Purification of Hormones Requires a Bioassay

How is a hormone discovered and isolated? First, researchers find that a physiological process in one tissue depends on a signal that originates in another tissue. Insulin, for example, was first recognized as a substance that is produced in the pancreas and affects the volume and composition of urine (Box 23–1). Once a physiological effect of the putative hormone is discovered, a quantitative bioassay for the hormone can be developed. In the case of insulin, the assay consisted of injecting extracts of pancreas (a crude source of insulin) into experimental animals deficient in insulin, then quantifying the resulting changes in glucose concentration in blood and urine. To isolate a hormone, the biochemist fractionates extracts containing the putative hormone, with the same techniques used to purify other biomolecules (solvent fractionation, chromatography, and electrophoresis), and then assays each fraction for hormone activity. Once the chemical has been purified, its composition and structure can be determined.

This protocol for hormone characterization is deceptively simple. Hormones are extremely potent and are produced in very small amounts. Obtaining sufficient hormone to allow its chemical characterization often involves biochemical isolations on a heroic scale. When Roger Guillemin and Andrew Schally independently purified and characterized thyrotropin-releasing hormone (TRH) from the hypothalamus, Schally's group processed about 20 tons of hypothalamus from nearly two million sheep, and Guillemin's group extracted the

FIGURE 23–1 Signaling by the neuroendocrine system. (a) In neuronal signaling, electrical signals (nerve impulses) originate in the cell body of a neuron and travel very rapidly over long distances to the axon tip, where neurotransmitters are released and diffuse to the target cell. The target cell (another neuron, a myocyte, or a secretory cell) is only a fraction of a micrometer or a few micrometers away from the site of neurotransmitter release. **(b)** In the endocrine system, hormones are secreted into the bloodstream, which carries them throughout the body to target tissues that may be a meter or more away from the secreting cell. Both neurotransmitters and hormones interact with specific receptors on or in their target cells, triggering responses.

BOX 23–1 BIOCHEMISTRY IN MEDICINE

How Is a Hormone Discovered? The Arduous Path to Purified Insulin

Millions of people with type I (insulin-dependent) diabetes mellitus inject themselves daily with pure insulin to compensate for the lack of production of this critical hormone by their own pancreatic β cells. Insulin injection is not a cure for diabetes, but it allows people who otherwise would have died young to lead long and productive lives. The discovery of insulin, which began with an accidental observation, illustrates the combination of serendipity and careful experimentation that led to the discovery of many of the hormones.

In 1889, Oskar Minkowski, a young assistant at the Medical College of Strasbourg, and Josef von Mering, at the Hoppe-Seyler Institute in Strasbourg, had a friendly disagreement about whether the pancreas, known to contain lipases, was important in fat digestion in dogs. To resolve the issue, they began an experiment on fat digestion. They surgically removed the pancreas from a dog, but before their experiment got any farther, Minkowski noticed that the dog was now producing far more urine than normal (a common symptom of untreated diabetes). Also, the dog's urine had glucose levels far above normal (another symptom of diabetes). These findings suggested that lack of some pancreatic product caused diabetes.

Minkowski tried unsuccessfully to prepare an extract of dog pancreas that would reverse the effect of removing the pancreas—that is, would lower the urinary or blood glucose levels. We now know that insulin is a protein, and that the pancreas is very rich in proteases (trypsin and chymotrypsin), normally released directly into the small intestine to aid in digestion. These proteases doubtless degraded the insulin in the pancreatic extracts in Minkowski's experiments.

Despite considerable effort, no significant progress was made in the isolation or characterization of the "antidiabetic factor" until the summer of 1921, when Frederick G. Banting, a young scientist working in the laboratory of J. J. R. MacLeod at the University of Toronto, and a student assistant, Charles Best, took up the problem. By that time, several lines of evidence pointed to a group of specialized cells in the pancreas (the islets of Langerhans; see Fig. 23–24) as the source of the antidiabetic factor, which came to be called insulin (from Latin *insula*, "island").

Taking precautions to prevent proteolysis, Banting and Best (later aided by biochemist J. B. Collip) succeeded in December 1921 in preparing a purified pancreatic extract that cured the symptoms of experimental diabetes in dogs. On January 25, 1922 (just one month later!), their insulin preparation was injected into Leonard Thompson, a 14-year-old boy severely ill with diabetes mellitus. Within days, the levels of ketone bodies and glucose in Thompson's urine dropped dramatically; the extract saved his life. In 1923, Banting and MacLeod won the Nobel Prize for their isolation of insulin. Banting immediately announced that he would share his prize with Best; MacLeod shared his with Collip.

By 1923, pharmaceutical companies were supplying thousands of patients throughout the world with insulin extracted from porcine pancreas. With the development of genetic engineering techniques in the 1980s (Chapter 9), it became possible to produce unlimited quantities of human insulin by inserting the cloned human gene for insulin in a microorganism, which was then cultured on an industrial scale. Some patients with diabetes are now fitted with implanted insulin pumps, which release adjustable amounts of insulin on demand to meet changing needs at meal times and during exercise. There is a reasonable prospect that, in the future, transplantation of pancreatic tissue will provide diabetic patients with a source of insulin that responds as well as normal pancreas, releasing insulin into the bloodstream only when blood glucose rises.

Frederick G. Banting, 1891–1941

J. J. R. MacLeod, 1876–1935

Charles Best, 1899–1978

J. B. Collip, 1892–1965

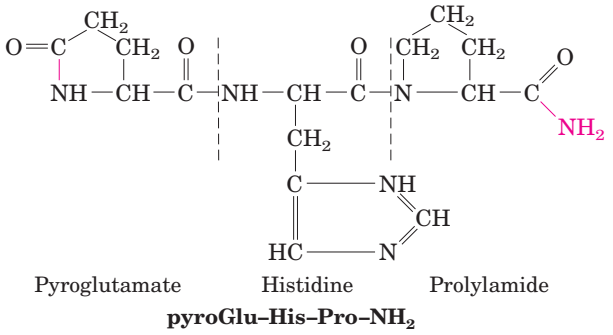


FIGURE 23–2 The structure of thyrotropin-releasing hormone (TRH). Purified (by heroic efforts) from extracts of hypothalamus, TRH proved to be a derivative of the tripeptide Glu–His–Pro. The side-chain carboxyl group of the amino-terminal Glu forms an amide (red bond) with the residue's α-amino group, creating pyroglutamate, and the carboxyl group of the carboxyl-terminal Pro is converted to an amide (red —NH_2). Such modifications are common among the small peptide hormones. In a typical protein of M_r ~50, the charges on the amino- and carboxyl-terminal groups contribute relatively little to the overall charge on the protein, but in a tripeptide these two charges dominate the properties of the peptide. Formation of the amide derivatives removes these charges.

hypothalamus from about a million pigs! TRH proved to be a simple derivative of the tripeptide Glu–His–Pro (Fig. 23–2). Once the structure of the hormone was known, it could be chemically synthesized in large quantities for use in physiological and biochemical studies.

For their work on hypothalamic hormones, Schally and Guillemin shared the Nobel Prize in Physiology or Medicine in 1977, along with Rosalyn Yalow, who (with Solomon A. Berson) developed the extraordinarily sensitive **radioimmunoassay (RIA)** for peptide hormones and used it to study hormone action. RIA revolutionized hormone research by making possible the rapid, quantitative, and specific measurement of hormones in minute amounts.

Hormone-specific antibodies are the key to the radioimmunoassay. Purified hormone, injected into rabbits, elicits antibodies that bind to that hormone with very high affinity and specificity. When a constant amount of isolated antibody is incubated with a fixed amount of the radioactively labeled hormone, a certain fraction of the radioactive hormone binds to the antibody (Fig. 23–3). If, in addition to the radiolabeled hormone, unlabeled hormone is also present, the unlabeled hormone competes with and displaces some of the labeled hormone from its binding site on the antibody. This binding competition can be quantified by reference to a standard curve obtained with known amounts of unlabeled hormone. The degree to which labeled hormone is displaced from antibody is a measure of the amount of unlabeled hormone in a sample of blood or tissue extract. By using very highly radioactive hormone, researchers can make the assay sensitive to picograms of hormone. A newer variation of this technique, enzyme-linked immunosorbent assay (ELISA), is illustrated in Figure 5–28b.

Hormones Act through Specific High-Affinity Cellular Receptors

As we saw in Chapter 12, all hormones act through highly specific receptors in hormone-sensitive target cells, to which the hormones bind with high affinity (see Fig. 12–2). Each cell type has its own combination of hormone receptors, which define the range of its hormone responsiveness. Moreover, two cell types with the same type of receptor may have different intracellular targets of hormone action and thus may respond differently to the same hormone. The specificity of hormone action results from structural complementarity between the hormone and its receptor; this interaction is extremely selective, so structurally similar hormones can have different effects. The high affinity of the interaction allows cells to respond to very low concentrations of hormone. In the design of drugs intended to intervene in hormonal regulation, we need to know the relative specificity and affinity of the drug and the natural hormone. Recall that hormone-receptor interactions can be quantified by **Scatchard analysis** (see Box 12–1), which, under favorable conditions, yields a quantitative measure of affinity (the dissociation constant for the complex) and the number of hormone-binding sites in a preparation of receptor.


Roger Guillemin


Andrew V. Schally


Rosalyn S. Yalow

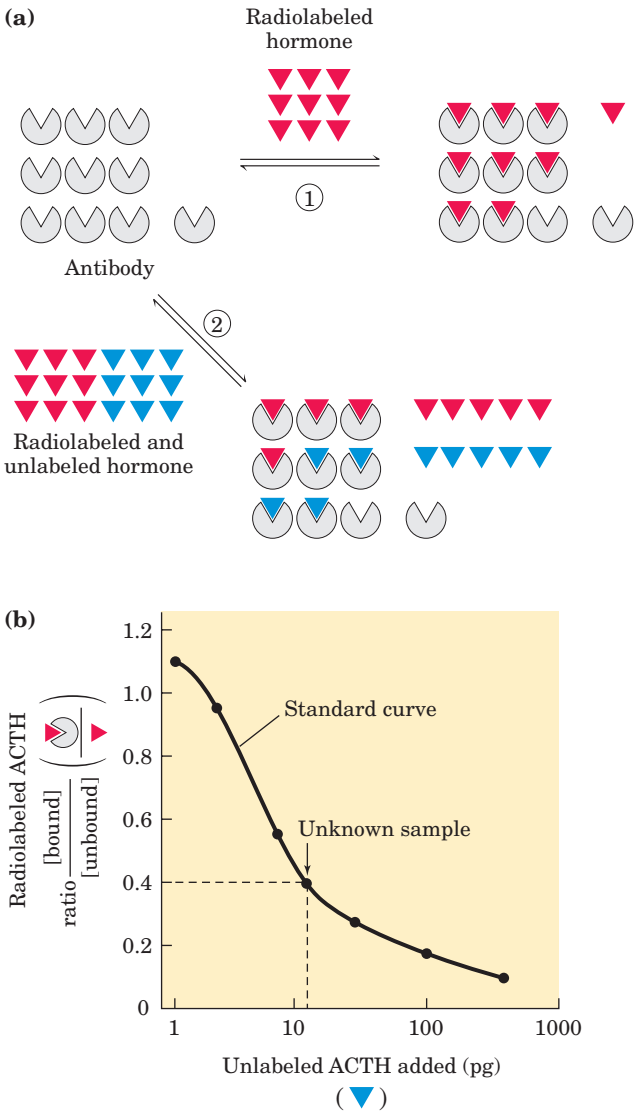


FIGURE 23–3 Radioimmunoassay (RIA). (a) A low concentration of radiolabeled hormone (red) is incubated with ① a fixed amount of antibody specific for that hormone or ② a fixed amount of antibody and various concentrations of unlabeled hormone (blue). In the latter case, unlabeled hormone competes with labeled hormone for binding to the antibody; the amount of labeled hormone bound varies inversely with the concentration of unlabeled hormone present. **(b)** A radioimmunoassay for adrenocorticotropic hormone (ACTH). A standard curve of the ratio [bound] to [unbound radiolabeled ACTH] vs. [unlabeled ACTH added] is constructed and used to determine the amount of (unlabeled) ACTH in an unknown sample. If an aliquot containing an unknown quantity of unlabeled hormone gives, say, a value of 0.4 for the ratio [bound]/[unbound] (see arrow), the aliquot must contain about 20 pg of ACTH.

The locus of the encounter between hormone and receptor may be extracellular, cytosolic, or nuclear, depending on the hormone type. The intracellular consequences of hormone-receptor interaction are of at least six general types: (1) a change in membrane potential results from the opening or closing of a hormone-gated ion channel; (2) a receptor enzyme is activated by the extracellular hormone; (3) a second messenger (such as cAMP or inositol trisphosphate) generated inside the cell acts as an allosteric regulator of one or more enzymes; (4) a receptor with no intrinsic enzyme activity recruits a soluble protein kinase in the cytosol, which passes on the signal; (5) an adhesion receptor on the cell surface interacts with molecules in the extracellular matrix and conveys information to the cytoskeleton; or (6) a steroid or steroidlike molecule causes a change in the level of expression (transcription of DNA into mRNA) of one or more genes, mediated by a nuclear hormone receptor protein (see Fig. 12–2).

Water-soluble peptide and amine hormones (insulin and epinephrine, for example) act extracellularly by binding to cell surface receptors that span the plasma membrane (Fig. 23–4). When the hormone binds to its extracellular domain, the receptor undergoes a conformational change analogous to that produced in an allosteric enzyme by binding of an effector molecule. The conformational change triggers the downstream effects of the hormone.

A single hormone molecule, in forming a hormone-receptor complex, activates a catalyst that produces many molecules of second messenger, so the receptor

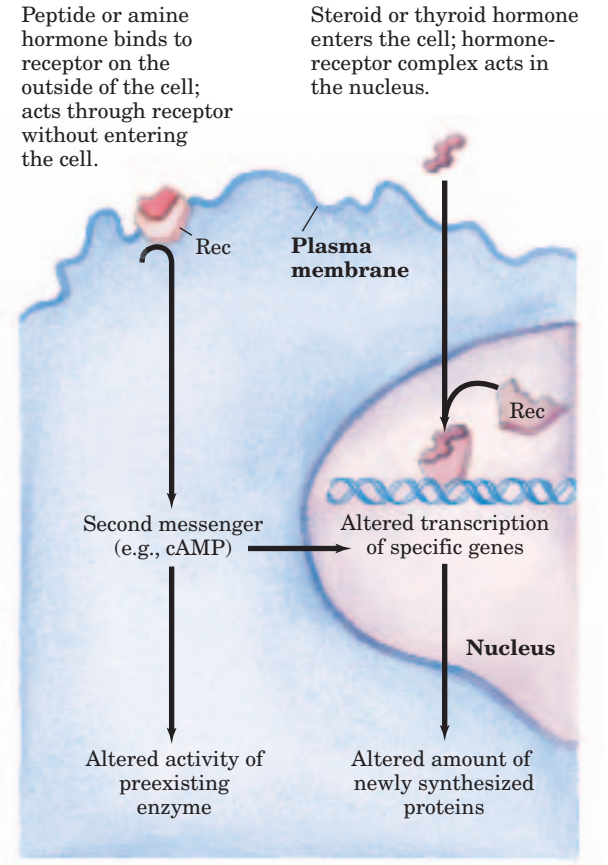


FIGURE 23–4 Two general mechanisms of hormone action. The peptide and amine hormones are faster acting than steroid and thyroid hormones.

serves not only as a signal transducer but also as a signal amplifier. The signal may be further amplified by a signaling cascade, a series of steps in which a catalyst activates a catalyst, resulting in very large amplifications of the original signal. A cascade of this type occurs in the regulation of glycogen synthesis and breakdown by epinephrine (see Fig. 12–16). Epinephrine activates (through its receptor) adenylyl cyclase, which produces many molecules of cAMP for each molecule of receptor-bound hormone. Cyclic AMP in turn activates cAMP-dependent protein kinase, which activates phosphorylase kinase, which activates glycogen phosphorylase. The result is signal amplification: one epinephrine molecule causes the production of many thousands of molecules of glucose 1-phosphate from glycogen.

Water-insoluble hormones (steroid, retinoid, and thyroid hormones) readily pass through the plasma membrane of their target cells to reach their receptor proteins in the nucleus (Fig. 23–4). With this class of hormones, the hormone-receptor complex itself carries the message; it interacts with DNA to alter the expression of specific genes, changing the enzyme complement of the cell and thereby changing cellular metabolism (see Fig. 12–40).

Hormones that act through plasma membrane receptors generally trigger very rapid physiological or biochemical responses. Just seconds after the adrenal medulla secretes epinephrine into the bloodstream, skeletal muscle responds by accelerating the breakdown of glycogen. By contrast, the thyroid hormones and the sex (steroid) hormones promote maximal responses in their target tissues only after hours or even days. These differences in response time correspond to different modes of action. In general, the fast-acting hormones lead to a change in the activity of one or more preexisting enzymes in the cell, by allosteric mechanisms or covalent modification. The slower-acting hormones generally alter gene expression, resulting in the synthesis of more or less of the regulated protein(s).

Hormones Are Chemically Diverse

Mammals have several classes of hormones, distinguishable by their chemical structures and their modes of action (Table 23–1). Peptide, amine, and eicosanoid hormones act from outside the target cell via surface receptors. Steroid, vitamin D, retinoid, and thyroid hormones enter the cell and act through nuclear receptors. Nitric oxide also enters the cell, but activates a cytosolic enzyme, guanylyl cyclase (see Fig. 12–10).

Hormones can also be classified by the way they get from the point of their release to their target tissue. **Endocrine** (from the Greek *endon,* "within," and *krinein,* "to release") hormones are released into the blood and carried to target cells throughout the body (insulin is an example). **Paracrine** hormones are released into the extracellular space and diffuse to neighboring target cells (the eicosanoid hormones are of this type). **Autocrine** hormones are released by and affect the same cell, binding to receptors on the cell surface.

Mammals are hardly unique in possessing hormonal signaling systems. Insects and nematode worms have highly developed systems for hormonal regulation, with fundamental mechanisms similar to those in mammals. Plants, too, use hormonal signals to coordinate the activities of their various tissues (Chapter 12). The study of hormone action is not as advanced in plants as in animals, but we do know that some mechanisms are shared. To illustrate the structural diversity and range of action of mammalian hormones, we consider representative examples of each major class listed in Table 23–1.

Peptide Hormones Peptide hormones may have from 3 to 200 or more amino acid residues. They include the pancreatic hormones insulin, glucagon, and somatostatin, the parathyroid hormone, calcitonin, and all the hormones of the hypothalamus and pituitary (described below). These hormones are synthesized on ribosomes in the form of longer precursor proteins (prohormones),

TABLE 23–1 Classes of Hormones

Type	*Example*	*Synthetic path*	*Mode of action*
Peptide	Insulin, glucagon	Proteolytic processing of prohormone	Plasma membrane receptors; second messengers
Catecholamine	Epinephrine	From tyrosine	
Eicosanoid	PGE_1	From arachidonate (20:4 fatty acid)	
Steroid	Testosterone	From cholesterol	Nuclear receptors; transcriptional regulation
Vitamin D	1,25-Dihydroxycholecalciferol	From cholesterol	
Retinoid	Retinoic acid	From vitamin A	
Thyroid	Triiodothyronine (T_3)	From Tyr in thyroglobulin	
Nitric oxide	Nitric oxide	From arginine + O_2	Cytosolic receptor (guanylate cyclase) and second messenger (cGMP)

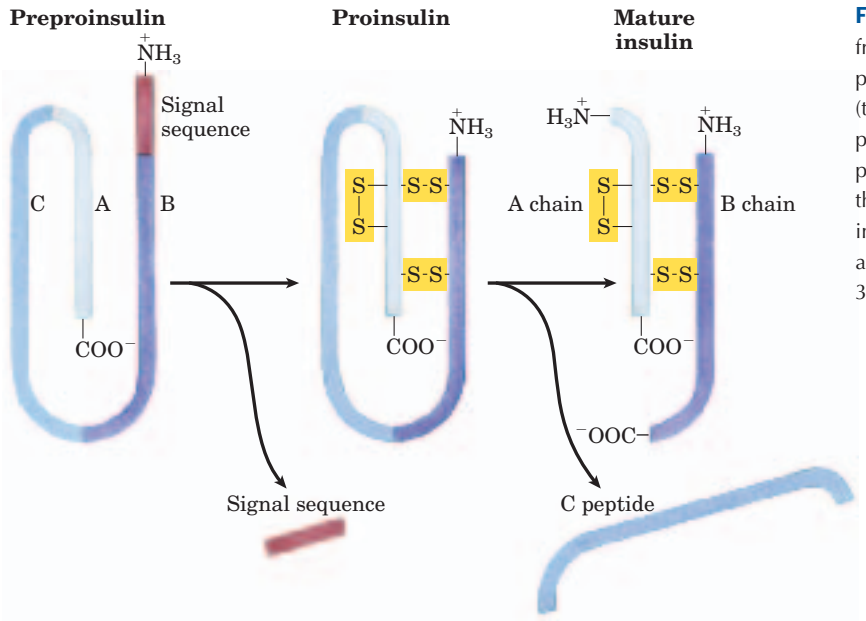


FIGURE 23–5 Insulin. Mature insulin is formed from its larger precursor preproinsulin by proteolytic processing. Removal of a 23 amino acid segment (the signal sequence) at the amino terminus of preproinsulin and formation of three disulfide bonds produces proinsulin. Further proteolytic cuts remove the C peptide from proinsulin to produce mature insulin, composed of A and B chains. The amino acid sequence of bovine insulin is shown in Figure 3–24.

then packaged into secretory vesicles and proteolytically cleaved to form the active peptides. **Insulin** is a small protein (M_r 5,800) with two polypeptide chains, A and B, joined by two disulfide bonds. It is synthesized in the pancreas as an inactive single-chain precursor, preproinsulin (Fig. 23–5), with an amino-terminal "signal sequence" that directs its passage into secretory vesicles. (Signal sequences are discussed in Chapter 27; see Fig. 27–33.) Proteolytic removal of the signal sequence and formation of three disulfide bonds produces proinsulin, which is stored in secretory granules in pancreatic β cells. When elevated blood glucose triggers insulin secretion, proinsulin is converted to active insulin by specific proteases, which cleave two peptide bonds to form the mature insulin molecule.

In some cases, prohormone proteins yield a single peptide hormone, but often several active hormones are carved out of the same prohormone. Pro-opiomelanocortin (POMC) is a spectacular example of multiple hormones encoded by a single gene. The POMC gene encodes a large polypeptide that is progressively carved up into at least nine biologically active peptides (Fig. 23–6). The terminal residues of peptide hormones are often modified, as in TRH (Fig. 23–2).

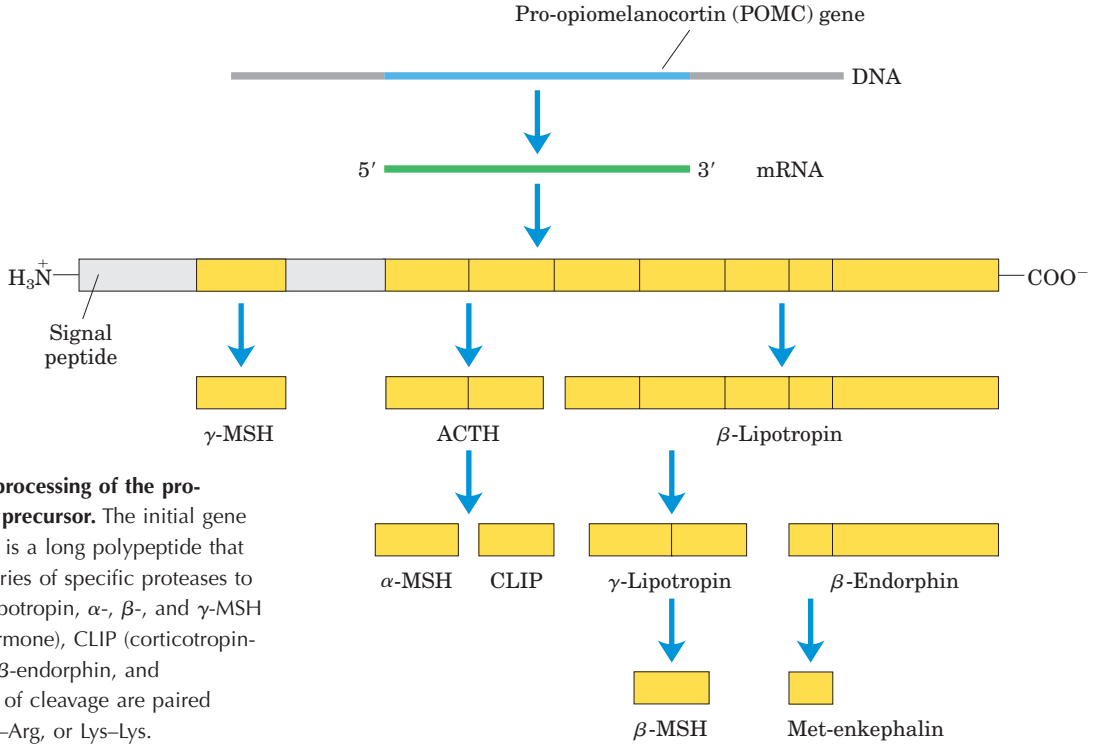


FIGURE 23–6 Proteolytic processing of the pro-opiomelanocortin (POMC) precursor. The initial gene product of the POMC gene is a long polypeptide that undergoes cleavage by a series of specific proteases to produce ACTH, β- and γ-lipotropin, α-, β-, and γ-MSH (melanocyte-stimulating hormone), CLIP (corticotropin-like intermediary peptide), β-endorphin, and Met-enkephalin. The points of cleavage are paired basic residues, Arg–Lys, Lys–Arg, or Lys–Lys.

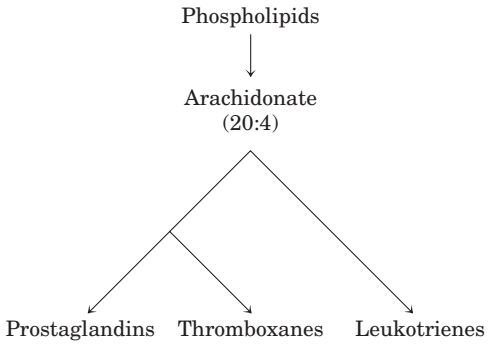
The concentration of peptide hormones within secretory granules is so high that the vesicle contents are virtually crystalline; when the contents are released by exocytosis, a large amount of hormone is released suddenly. The capillaries that serve peptide-producing endocrine glands are fenestrated (and thus permeable to peptides), so the hormone molecules readily enter the bloodstream for transport to target cells elsewhere. As noted earlier, all peptide hormones act by binding to receptors in the plasma membrane. They cause the generation of a second messenger in the cytosol, which changes the activity of an intracellular enzyme, thereby altering the cell's metabolism.

Catecholamine Hormones The water-soluble compounds **epinephrine (adrenaline)** and **norepinephrine (noradrenaline)** are **catecholamines,** named for the structurally related compound catechol. They are synthesized from tyrosine.

Tyrosine ⟶ L-DOPA ⟶ Dopamine ⟶ Norepinephrine ⟶ Epinephrine

Catecholamines produced in the brain and in other neural tissues function as neurotransmitters, but epinephrine and norepinephrine are also hormones, synthesized and secreted by the adrenal glands. Like the peptide hormones, catecholamines are highly concentrated within secretory vesicles and released by exocytosis, and they act through surface receptors to generate intracellular second messengers. They mediate a wide variety of physiological responses to acute stress (see Table 23–6).

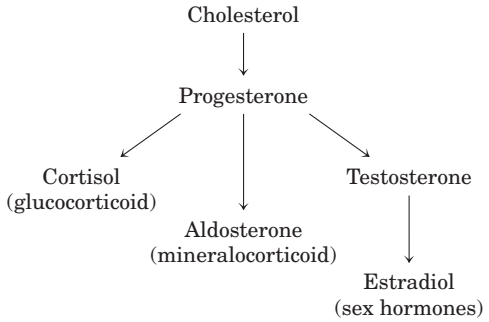
Eicosanoids The eicosanoid hormones (prostaglandins, thromboxanes, and leukotrienes) are derived from the 20-carbon polyunsaturated fatty acid arachidonate.



Unlike the hormones described above, they are not synthesized in advance and stored; they are produced, when needed, from arachidonate enzymatically released from membrane phospholipids by phospholipase A_2 (see Fig. 10–18). The enzymes of the pathway leading to prostaglandins and thromboxanes (see Fig. 21–15) are very widely distributed in mammalian tissues; most cells can produce these signals, and cells of many tissues can respond to them through specific plasma membrane receptors. The eicosanoid hormones are paracrine hormones, secreted into the interstitial fluid (not primarily into the blood) and acting on nearby cells.

Prostaglandins promote the contraction of smooth muscle, including that of the intestine and uterus (and can therefore be used medically to induce labor). They also mediate pain and inflammation in all tissues. Many antiinflammatory drugs act by inhibiting steps in the prostaglandin synthetic pathway (see Box 21–2). Thromboxanes regulate platelet function and therefore blood clotting. Leukotrienes LTC_4 and LTD_4 act through plasma membrane receptors to stimulate contraction of smooth muscle in the intestine, pulmonary airways, and trachea. They are mediators of the severe immune response called anaphylaxis. ■

Steroid Hormones The steroid hormones (adrenocortical hormones and sex hormones) are synthesized from cholesterol in several endocrine tissues.



They travel to their target cells through the bloodstream, bound to carrier proteins. More than 50 corticosteroid hormones are produced in the adrenal cortex by reactions that remove the side chain from the D ring of cholesterol and introduce oxygen to form keto and hydroxyl groups. Many of these reactions involve cytochrome P-450 enzymes (see Box 21–1). The steroid hormones are of two general types. Glucocorticoids (such as cortisol) primarily affect the metabolism of carbohydrates; mineralocorticoids (such as aldosterone) regulate the concentrations of electrolytes in the blood. Androgens (testosterone) and estrogens (such as estradiol; see Fig. 10–19) are synthesized in the testes and ovaries. Their synthesis also involves cytochrome P-450 enzymes that cleave the side chain of cholesterol and introduce oxygen atoms. These hormones affect sexual development, sexual behavior, and a variety of other reproductive and nonreproductive functions.

All steroid hormones act through nuclear receptors to change the level of expression of specific genes (p. 465). Recent evidence indicates that they also have more rapid effects, mediated by receptors localized in the plasma membrane.

Vitamin D Hormone Calcitriol (1,25-dihydroxycholecalciferol) is produced from vitamin D by enzyme-catalyzed hydroxylation in the liver and kidneys (see Fig. 10–20a).

7-Dehydrocholesterol
↓ UV light
Vitamin D_3 (cholecalciferol)
↓
25-Hydroxycholecalciferol
↓
1,25-Dihydroxycholecalciferol

Vitamin D is obtained in the diet or by photolysis of 7-dehydrocholesterol in skin exposed to sunlight. Calcitriol works in concert with parathyroid hormone in Ca^{2+} homeostasis, regulating $[Ca^{2+}]$ in the blood and the balance between Ca^{2+} deposition and Ca^{2+} mobilization from bone. Acting through nuclear receptors, calcitriol activates the synthesis of an intestinal Ca^{2+}-binding protein essential for uptake of dietary Ca^{2+}. Inadequate dietary vitamin D or defects in the biosynthesis of calcitriol result in serious diseases such as rickets, in which bones are weak and malformed (see Fig. 10–20b).

Retinoid Hormones Retinoids are potent hormones that regulate the growth, survival, and differentiation of cells via nuclear retinoid receptors. The prohormone retinol is synthesized from vitamin A, primarily in liver (see Fig. 10–21), and many tissues convert retinol to the hormone retinoic acid (RA).

β-Carotene
↓
Vitamin A_1 (retinol)
↓
Retinoic acid

All tissues are retinoid targets, as all cell types have at least one form of nuclear retinoid receptor. In adults, the most significant targets include cornea, skin, epithelia of the lungs and trachea, and the immune system. RA regulates the synthesis of proteins essential for growth or differentiation. Excessive vitamin A can cause birth defects, and pregnant women are advised not to use the retinoid creams that have been developed for treatment of severe acne.

Thyroid Hormones The thyroid hormones T_4 (thyroxine) and T_3 (triiodothyronine) are synthesized from the precursor protein thyroglobulin (M_r 660,000). Up to 20 Tyr residues in thyroglobulin are enzymatically iodinated in the thyroid gland, then two iodotyrosine residues condense to form the precursor to thyroxine. When needed, thyroxine is released by proteolysis. Condensation of monoiodotyrosine with diiodotyrosine produces T_3, which is also an active hormone released by proteolysis.

Thyroglobulin–Tyr
↓
Thyroglobulin–Tyr–I (iodinated Tyr residues)
↓ proteolysis
Thyroxine (T_4), triiodothyronine (T_3)

The thyroid hormones act through nuclear receptors to stimulate energy-yielding metabolism, especially in liver and muscle, by increasing the expression of genes encoding key catabolic enzymes.

Nitric Oxide (NO) Nitric oxide is a relatively stable free radical synthesized from molecular oxygen and the guanidino nitrogen of arginine (see Fig. 22–31) in a reaction catalyzed by **NO synthase.**

$$\text{Arginine} + 1\tfrac{1}{2}\ \text{NADPH} + 2O_2 \longrightarrow \text{NO} + \text{citrulline} + 2H_2O + 1\tfrac{1}{2}\ \text{NADP}^+$$

This enzyme is found in many tissues and cell types: neurons, macrophages, hepatocytes, myocytes of smooth muscle, endothelial cells of the blood vessels, and epithelial cells of the kidney. NO acts near its point of release, entering the target cell and activating the cytosolic enzyme guanylyl cyclase, which catalyzes the formation of the second messenger cGMP (see Fig. 12–10).

Hormone Release Is Regulated by a Hierarchy of Neuronal and Hormonal Signals

The changing levels of specific hormones regulate specific cellular processes, but what regulates the level of each hormone? The brief answer is that the central nervous system receives input from many internal and external sensors—signals about danger, hunger, dietary intake, blood composition and pressure, for example—and orchestrates the production of appropriate hormonal signals by the endocrine tissues. For a more complete answer, we must look at the hormone-producing systems of the human body and some of their functional interrelationships.

Figure 23–7 shows the anatomic location of the major endocrine glands in humans, and Figure 23–8 represents the "chain of command" in the hormonal signaling hierarchy. The **hypothalamus,** a small region of the brain (Fig. 23–9), is the coordination center of the

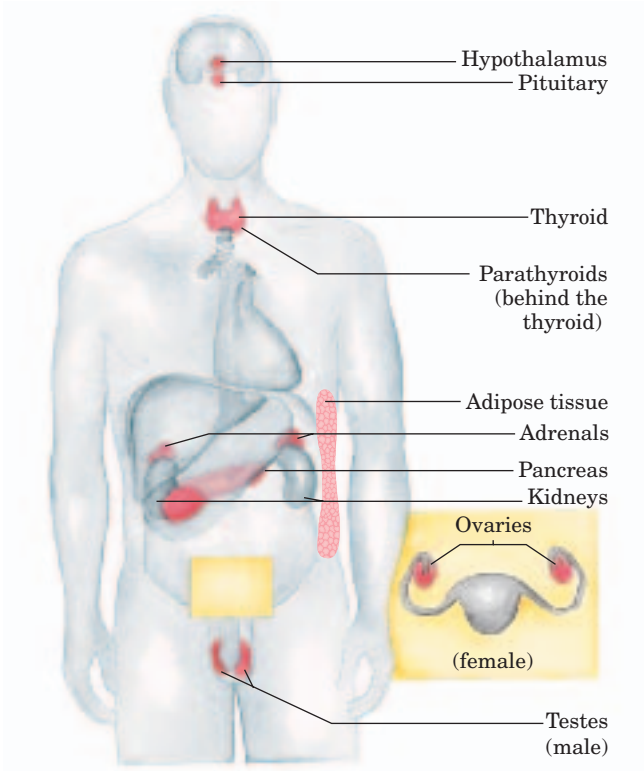


FIGURE 23–7 The major endocrine glands. The glands are shaded dark pink.

endocrine system; it receives and integrates messages from the central nervous system. In response to these messages, the hypothalamus produces regulatory hormones (releasing factors) that pass directly to the nearby pituitary gland, through special blood vessels and neurons that connect the two glands (Fig. 23–9b). The pituitary gland has two functionally distinct parts. The **posterior pituitary** contains the axonal endings of many neurons that originate in the hypothalamus. These neurons produce the short peptide hormones oxytocin and vasopressin (Fig. 23–10), which then move down the axon to the nerve endings in the pituitary, where they are stored in secretory granules to await the signal for their release.

The **anterior pituitary** responds to hypothalamic hormones carried in the blood, producing **tropic hormones,** or **tropins** (from the Greek *tropos,* "turn"). These relatively long polypeptides activate the next rank of endocrine glands (Fig. 23–8), which includes the adrenal cortex, thyroid gland, ovaries, and testes. These glands in turn secrete their specific hormones, which are carried in the bloodstream to the receptors of cells in the target tissues. For example, corticotropin-releasing hormone from the hypothalamus stimulates the anterior pituitary to release ACTH, which travels to the zona fasciculata of the adrenal cortex and triggers the release of

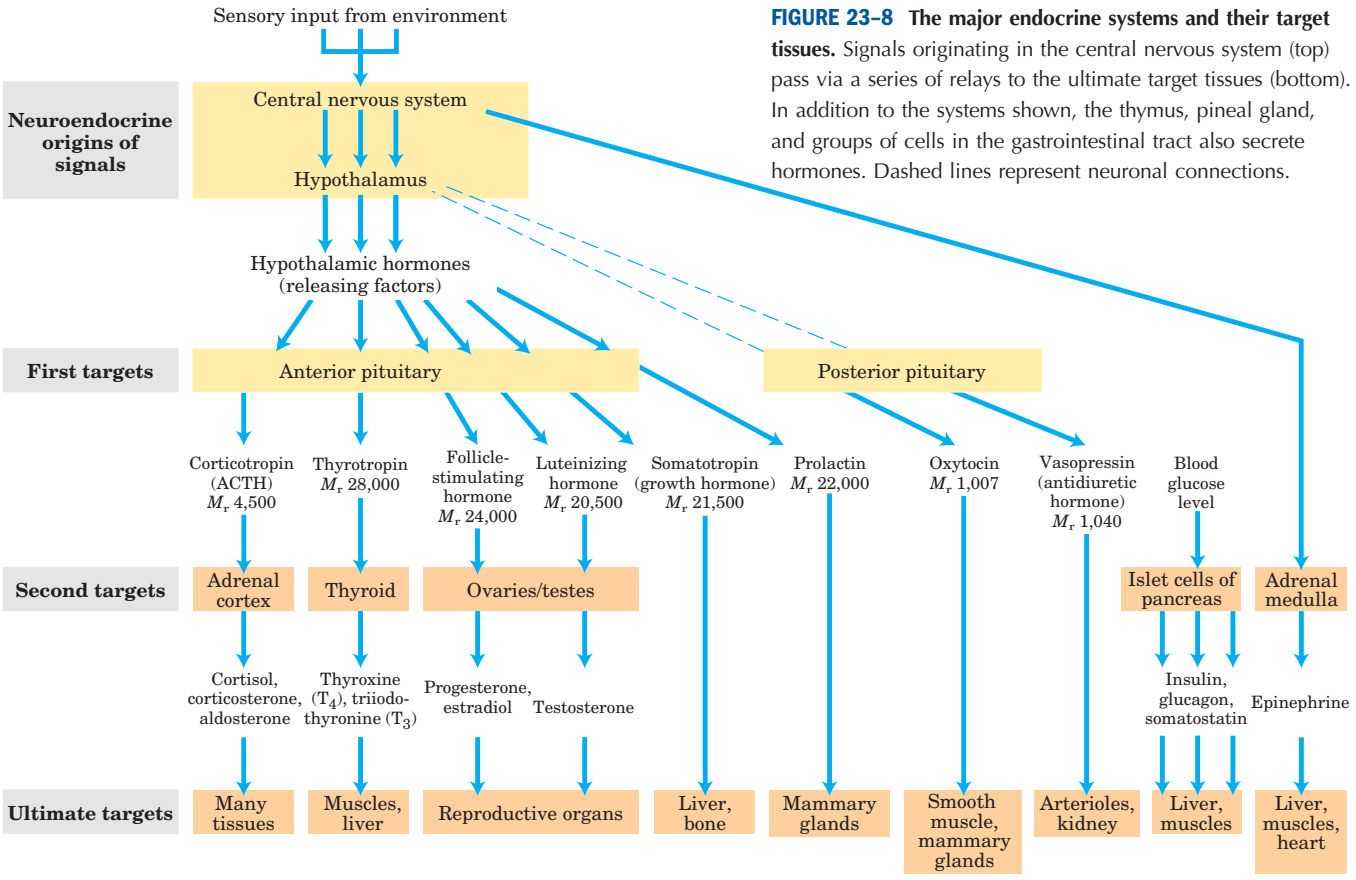


FIGURE 23–8 The major endocrine systems and their target tissues. Signals originating in the central nervous system (top) pass via a series of relays to the ultimate target tissues (bottom). In addition to the systems shown, the thymus, pineal gland, and groups of cells in the gastrointestinal tract also secrete hormones. Dashed lines represent neuronal connections.

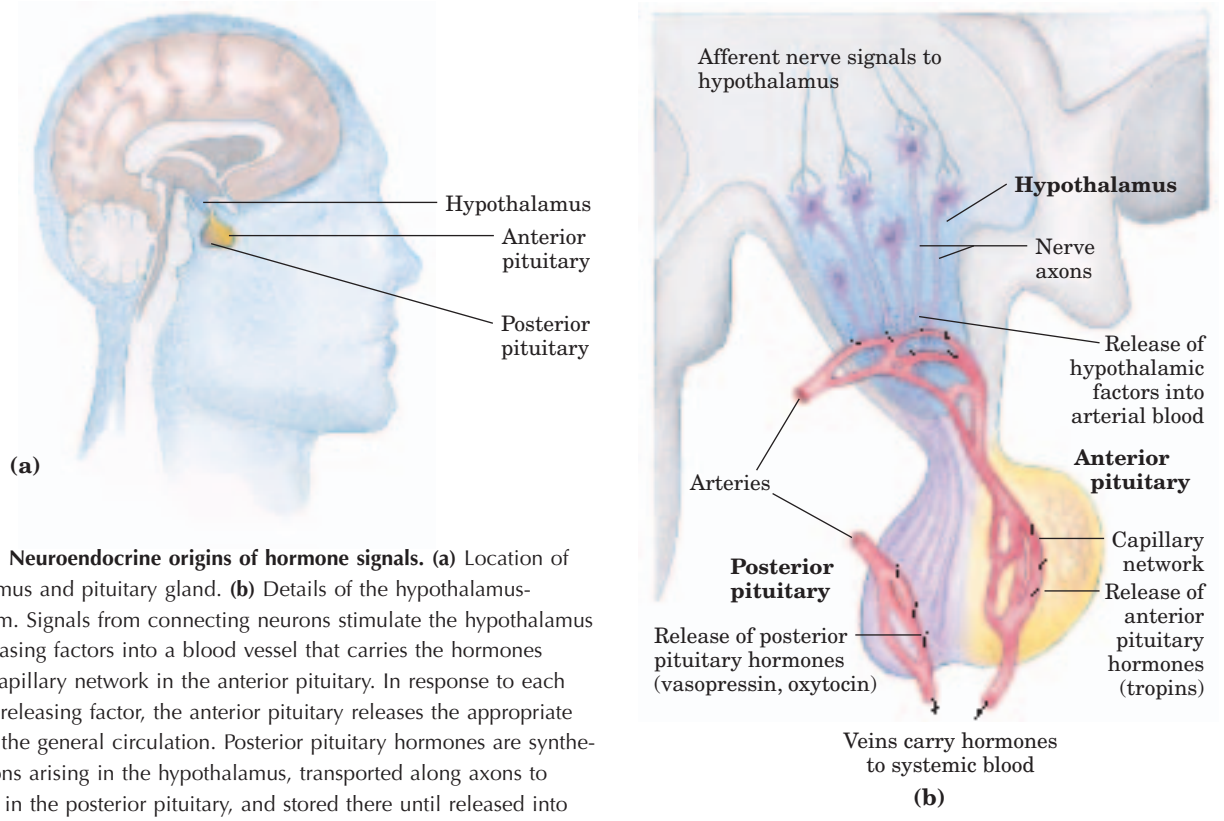


FIGURE 23–9 **Neuroendocrine origins of hormone signals.** **(a)** Location of the hypothalamus and pituitary gland. **(b)** Details of the hypothalamus-pituitary system. Signals from connecting neurons stimulate the hypothalamus to secrete releasing factors into a blood vessel that carries the hormones directly to a capillary network in the anterior pituitary. In response to each hypothalamic releasing factor, the anterior pituitary releases the appropriate hormone into the general circulation. Posterior pituitary hormones are synthesized in neurons arising in the hypothalamus, transported along axons to nerve endings in the posterior pituitary, and stored there until released into the blood in response to a neuronal signal.

cortisol. Cortisol, the ultimate hormone in this cascade, acts through its receptor in many types of target cells to alter their metabolism. In hepatocytes, one effect of cortisol is to increase the rate of gluconeogenesis.

Hormonal cascades such as those responsible for the release of cortisol and epinephrine result in large amplifications of the initial signal and allow exquisite fine-tuning of the output of the ultimate hormone (Fig. 23–11). At each level in the cascade, a small signal elicits a larger response. The initial electrical signal to the hypothalamus results in the release of a few *nanograms* of corticotropin-releasing hormone, which elicits the release of a few *micrograms* of corticotropin. Corticotropin acts on the adrenal cortex to cause the release of *milligrams* of cortisol, for an overall amplification of at least a millionfold.

At each level of a hormonal cascade, feedback inhibition of earlier steps in the cascade is possible; an unnecessarily elevated level of the ultimate hormone or of one of the intermediate hormones inhibits the release of earlier hormones in the cascade. These feedback mechanisms accomplish the same end as those that limit the output of a biosynthetic pathway (compare Fig. 23–11 with Fig. 6–28): a product is synthesized (or released) only until the necessary concentration is reached.

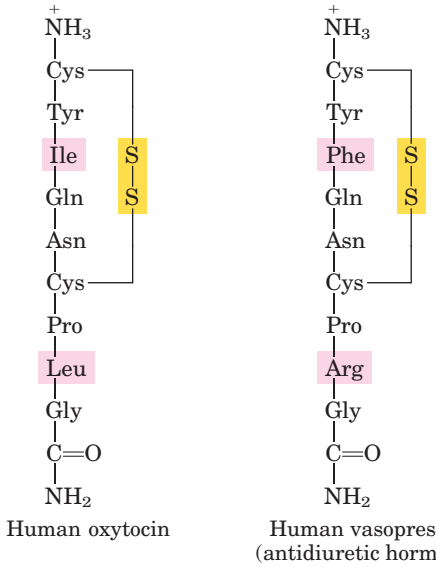


FIGURE 23–10 **Two hormones of the posterior pituitary gland.** The carboxyl-terminal residues are glycinamide, $—NH—CH_2—CONH_2$ (as noted in Fig. 23–2, amidation of the carboxyl terminus is common in short peptide hormones). These two hormones, identical in all but two residues (shaded), have very different biological effects. Oxytocin acts on the smooth muscles of the uterus and mammary gland, causing uterine contractions during labor and promoting milk release during lactation. Vasopressin (also called antidiuretic hormone) increases water reabsorption in the kidney and promotes the constriction of blood vessels, thereby increasing blood pressure.

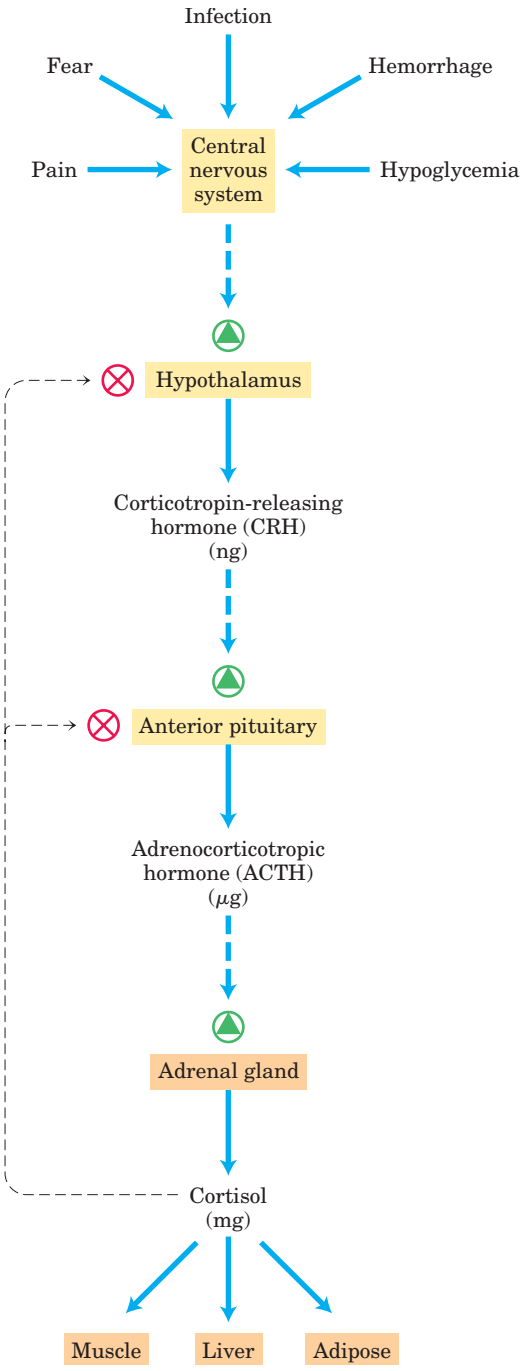


FIGURE 23–11 Cascade of hormone release following central nervous system input to the hypothalamus. In each endocrine tissue along the pathway, a stimulus from the level above is received, amplified, and transduced into the release of the next hormone in the cascade. The cascade is sensitive to regulation at several levels through feedback inhibition by the ultimate hormone. The product therefore regulates its own production, as in feedback inhibition of biosynthetic pathways within a single cell.

SUMMARY 23.1 Hormones: Diverse Structures for Diverse Functions

- Hormones are chemical messengers secreted by certain tissues into the blood or interstitial fluid, serving to regulate the activity of other cells or tissues.
- Radioimmunoassay (RIA) and ELISA are two very sensitive techniques for detecting and quantifying hormones.
- Hormonal cascades, in which catalysts activate catalysts, amplify the initial stimulus by several orders of magnitude, often in a very short time (seconds).
- Nerve impulses stimulate the hypothalamus to send specific hormones to the pituitary gland, thus stimulating (or inhibiting) the release of tropic hormones. The anterior pituitary hormones in turn stimulate other endocrine glands (thyroid, adrenals, pancreas) to secrete their characteristic hormones, which in turn stimulate specific target tissues.
- Peptide, amine, and eicosanoid hormones act outside the target cell on specific receptors in the plasma membrane, altering the level of an intracellular second messenger.
- Steroid, vitamin D, retinoid, and thyroid hormones enter target cells and alter gene expression by interacting with specific nuclear receptors.

23.2 Tissue-Specific Metabolism: The Division of Labor

Each tissue of the human body has a specialized function, reflected in its anatomy and metabolic activity (Fig. 23–12). Skeletal muscle allows directed motion; adipose tissue stores and releases energy in the form of fats, which serve as fuel throughout the body; the brain pumps ions across plasma membranes to produce electrical signals. The liver plays a central processing and distributing role in metabolism and furnishes all other organs and tissues with an appropriate mix of nutrients via the bloodstream. The functional centrality of the liver is indicated by the common reference to all other tissues and organs as "extrahepatic" or "peripheral." We therefore begin our discussion of the division of metabolic labor by considering the transformations of carbohydrates, amino acids, and fats in the mammalian liver. This is followed by brief descriptions of the primary metabolic functions of adipose tissue, muscle, brain, and the medium that interconnects all others: the blood.

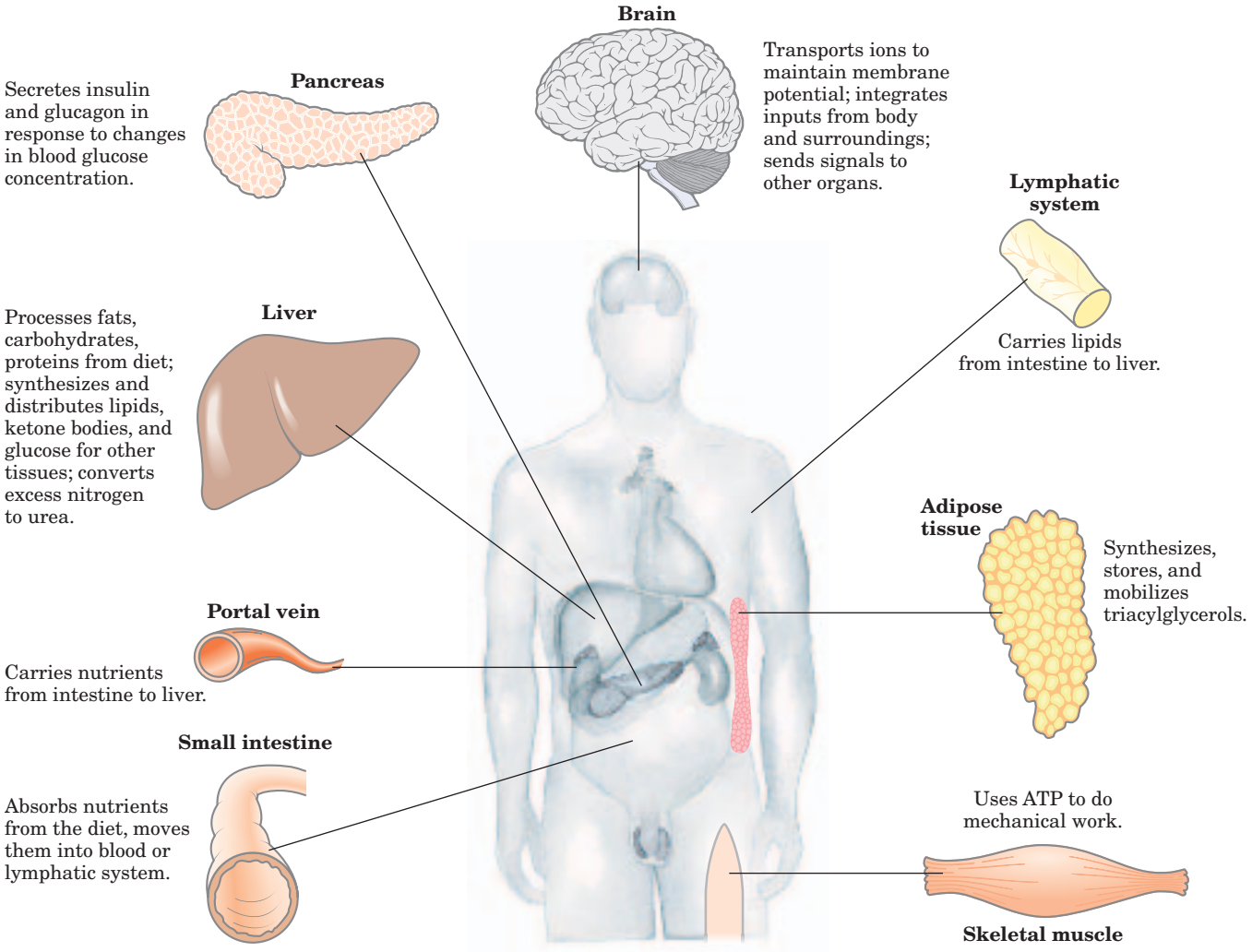


FIGURE 23–12 Specialized metabolic functions of mammalian tissues.

The Liver Processes and Distributes Nutrients

During digestion in mammals, the three main classes of nutrients (carbohydrates, proteins, and fats) undergo enzymatic hydrolysis into their simple constituents. This breakdown is necessary because the epithelial cells lining the intestinal lumen absorb only relatively small molecules. Many of the fatty acids and monoacylglycerols released by digestion of fats in the intestine are reassembled within these epithelial cells into triacylglycerols (TAGs).

After being absorbed, most sugars and amino acids and some TAGs travel in the bloodstream to the liver; the remaining TAGs enter adipose tissue via the lymphatic system. The portal vein is a direct route from the digestive organs to the liver, and liver therefore has first access to ingested nutrients. The liver has two main cell types. Kupffer cells are phagocytes, important in immune function. **Hepatocytes,** of primary interest here, transform dietary nutrients into the fuels and precursors required by other tissues and export them via the blood. The kinds and amounts of nutrients supplied to the liver vary with several factors, including the diet and the time between meals. The demand of extrahepatic tissues for fuels and precursors varies among organs and with the level of activity and overall nutritional state of the individual.

To meet these changing circumstances, the liver has remarkable metabolic flexibility. For example, when the diet is rich in protein, hepatocytes supply themselves with high levels of enzymes for amino acid catabolism and gluconeogenesis. Within hours after a shift to a high-carbohydrate diet, the levels of these enzymes begin to drop and the hepatocytes increase their synthesis of enzymes essential to carbohydrate metabolism and fat synthesis. Liver enzymes turn over (are synthesized and degraded) at five to ten times the rate of enzyme turnover in other tissues, such as muscle. Extrahepatic

TABLE 23–2 Pathways of Carbohydrate, Amino Acid, and Fat Metabolism Illustrated in Earlier Chapters

Pathway	*Figure reference*
Citric acid cycle: acetyl-CoA ⟶ $2CO_2$	16–7
Oxidative phosphorylation: ATP synthesis	19–17
Carbohydrate catabolism	
Glycogenolysis: glycogen ⟶ glucose 1-phosphate ⟶ blood glucose	15–3; 15–4
Hexose entry into glycolysis: fructose, mannose, galactose ⟶ glucose 6-phosphate	14–9
Glycolysis: glucose ⟶ pyruvate	14–2
Pyruvate dehydrogenase reaction: pyruvate ⟶ acetyl-CoA	16–2
Lactic acid fermentation: glucose ⟶ lactate + 2ATP	14–3
Pentose phosphate pathway: glucose 6-phosphate ⟶ pentose phosphates + NADPH	14–21
Carbohydrate anabolism	
Gluconeogenesis: citric acid cycle intermediates ⟶ glucose	14–16
Glucose-alanine cycle: glucose ⟶ pyruvate ⟶ alanine ⟶ glucose	18–9
Glycogen synthesis: glucose 6-phosphate ⟶ glucose 1-phosphate ⟶ glycogen	15–8
Amino acid and nucleotide metabolism	
Amino acid degradation: amino acids ⟶ acetyl-CoA, citric acid cycle intermediates	18–15
Amino acid synthesis	22–9
Urea cycle: NH_3 ⟶ urea	18–10
Glucose-alanine cycle: alanine ⟶ glucose	18–9
Nucleotide synthesis: amino acids ⟶ purines, pyrimidines	22–33; 22–36
Hormone and neurotransmitter synthesis	22–29
Fat catabolism	
β Oxidation of fatty acids: fatty acid ⟶ acetyl-CoA	17–8
Oxidation of ketone bodies: β-hydroxybutyrate ⟶ acetyl-CoA ⟶ CO_2 citric acid cycle	17–19
Fat anabolism	
Fatty acid synthesis: acetyl-CoA ⟶ fatty acids	21–5
Triacylglycerol synthesis: acetyl-CoA ⟶ fatty acids ⟶ triacylglycerol	21–18; 21–19
Ketone body formation: acetyl-CoA ⟶ acetoacetate, β-hydroxybutyrate	17–18
Cholesterol and cholesteryl ester synthesis: acetyl-CoA ⟶ cholesterol ⟶ cholesteryl esters	21–33 to 21–37
Phospholipid synthesis: fatty acids ⟶ phospholipids	21–17; 21–23 to 21–28

tissues also can adjust their metabolism to prevailing conditions, but none is as adaptable as the liver, and none is so central to the organism's overall metabolism. What follows is a survey of the possible fates of sugars, amino acids, and lipids that enter the liver from the bloodstream. To help you recall the metabolic transformations discussed here, Table 23–2 shows the major pathways and processes to which we refer and indicates by figure number where each pathway is presented in detail. Here, we present summaries of the pathways, referring to the step numbers in Figures 23–13 to 23–15.

Sugars The glucose transporter in hepatocytes (GLUT2) is so effective that the concentration of glucose within a hepatocyte is essentially the same as that in the blood. Glucose entering hepatocytes is phosphorylated by hexokinase IV (glucokinase) to yield glucose 6-phosphate. Glucokinase has a much higher K_m for glucose (10 mM) than do the hexokinase isozymes in other cells (p. 578) and, unlike these other isozymes, it is not inhibited by its product, glucose 6-phosphate. The presence of glucokinase allows hepatocytes to continue phosphorylating glucose when the glucose concentration rises well above levels that would overwhelm other hexokinases. The high K_m of glucokinase also ensures that the phosphorylation of glucose in hepatocytes is minimal when the glucose concentration is low, preventing the liver from consuming glucose as fuel via glycolysis. This spares glucose for other tissues. Fructose, galactose, and mannose, all absorbed from the small intestine, are also converted to glucose 6-phosphate by enzymatic pathways examined in Chapter 14. Glucose 6-phosphate is at the crossroads of carbohydrate metabolism in the liver. It may take any of several major metabolic routes (Fig. 23–13), depending on the current metabolic needs of the organism. By the action of various allosterically regulated enzymes, and through hormonal regulation of enzyme synthesis and activity, the liver directs the flow of glucose into one or more of these pathways.

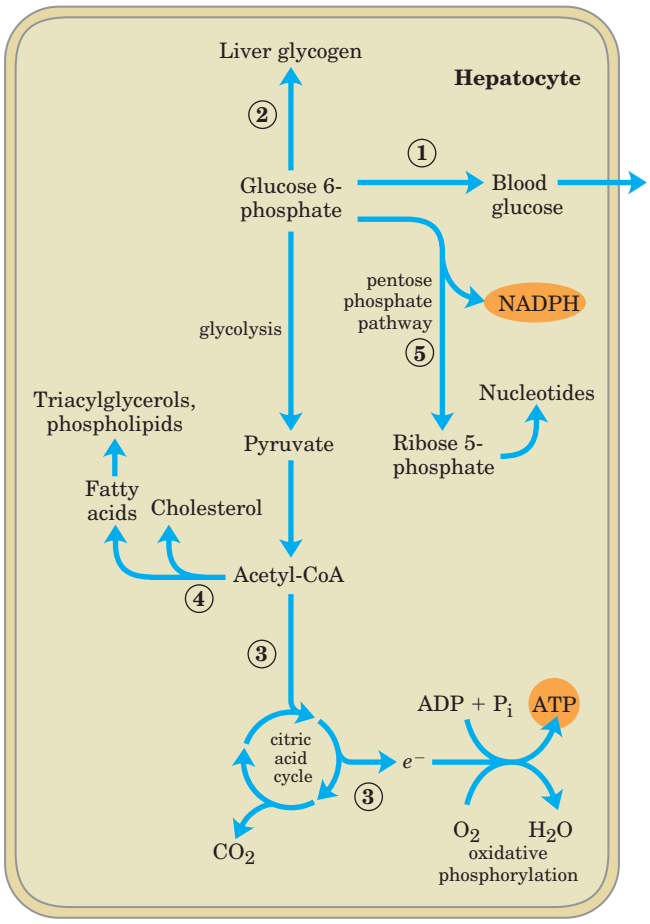


FIGURE 23–13 Metabolic pathways for glucose 6-phosphate in the liver. Here and in Figures 23–14 and 23–15, anabolic pathways are shown leading upward, catabolic pathways leading downward, and distribution to other organs horizontally. The numbered processes in each figure are described in the text.

(1) Glucose 6-phosphate is dephosphorylated by glucose 6-phosphatase to yield free glucose (p. 547), which is exported to replenish blood glucose. Export is the predominant pathway when glucose 6-phosphate is in limited supply, because the blood glucose concentration must be kept sufficiently high (4 mM) to provide adequate energy for the brain and other tissues. (2) Glucose 6-phosphate not immediately needed to form blood glucose is converted to liver glycogen, or it has one of several other fates. Following glucose 6-phosphate breakdown by glycolysis and decarboxylation of the pyruvate (by the pyruvate dehydrogenase reaction), (3) the acetyl-CoA so formed can be oxidized for energy production by the citric acid cycle, with ensuing electron transfer and oxidative phosphorylation yielding ATP. (Normally, however, fatty acids are the preferred fuel for energy production in hepatocytes.) (4) Acetyl-CoA can also serve as the precursor of fatty acids, which are incorporated into TAGs and phospholipids, and cholesterol. Much of the lipid synthesized in the liver is transported to other tissues by blood lipoproteins. (5) Finally, glucose 6-phosphate can enter the pentose phosphate pathway, yielding both reducing power (NADPH), needed for the biosynthesis of fatty acids and cholesterol, and D-ribose 5-phosphate, a precursor for nucleotide biosynthesis. NADPH is also an essential cofactor in the detoxification and elimination of many drugs and other xenobiotics metabolized in the liver.

Amino Acids Amino acids that enter the liver follow several important metabolic routes (Fig. 23–14). (1) They are precursors for protein synthesis, a process discussed in Chapter 27. The liver constantly renews its own proteins, which have a relatively high turnover rate (average half-life of only a few days), and is also the site of biosynthesis of most plasma proteins. (2) Alternatively, amino acids pass in the bloodstream to other organs, to be used in the synthesis of tissue proteins. (3) Other amino acids are precursors in the biosynthesis of nucleotides, hormones, and other nitrogenous compounds in the liver and other tissues.

(4a) Amino acids not needed as biosynthetic precursors are transaminated or deaminated and degraded to yield pyruvate and citric acid cycle intermediates, with various fates; (4b) the ammonia released is converted to the excretory product urea. (5) Pyruvate can be converted to glucose and glycogen via gluconeogenesis or (6) it can be converted to acetyl-CoA, which has several possible fates. (7) It can be oxidized via the citric acid cycle and (8) oxidative phosphorylation to produce ATP, or (9) converted to lipids for storage. (10) Citric acid cycle intermediates can be siphoned off into glucose synthesis by gluconeogenesis.

The liver also metabolizes amino acids that arrive intermittently from other tissues. The blood is adequately supplied with glucose just after the digestion and absorption of dietary carbohydrate or, between meals, by the conversion of liver glycogen to blood glucose. During the interval between meals, especially if prolonged, some muscle protein is degraded to amino acids. These amino acids donate their amino groups (by transamination) to pyruvate, the product of glycolysis, to yield alanine, which (11) is transported to the liver and deaminated. Hepatocytes convert the resulting pyruvate to blood glucose (via gluconeogenesis (5)), and the ammonia to urea for excretion. One benefit of this glucose-alanine cycle (see Fig. 18–9) is the smoothing out of fluctuations in blood glucose between meals. The amino acid deficit incurred in the muscles is made up after the next meal by incoming dietary amino acids.

Lipids The fatty acid components of the lipids entering hepatocytes also have several different fates (Fig. 23–15). (1) Some are converted to liver lipids. (2) Under most circumstances, fatty acids are the primary oxidative fuel in the liver. Free fatty acids may be activated

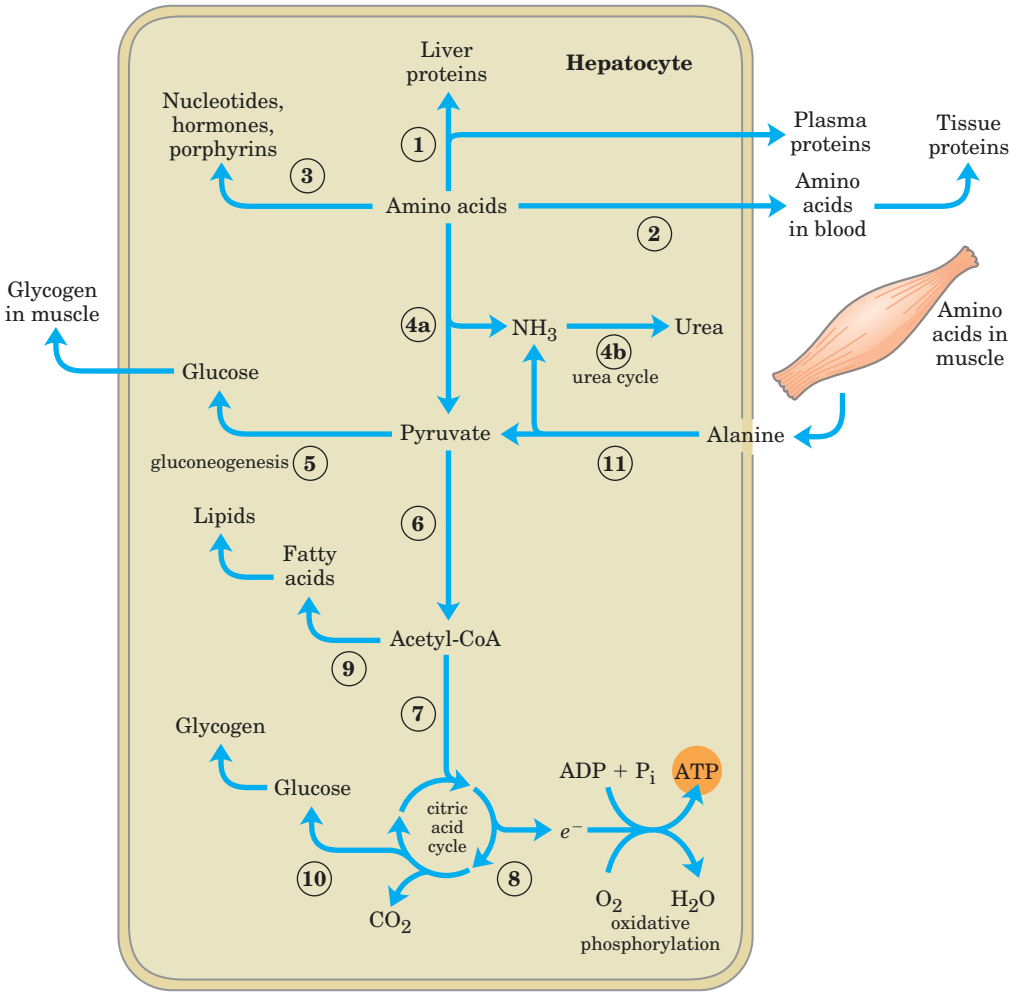


FIGURE 23–14 Metabolism of amino acids in the liver.

and oxidized to yield acetyl-CoA and NADH. (3) and (4) The acetyl-CoA is further oxidized via the citric acid cycle, and the oxidations in the cycle drive the synthesis of ATP by oxidative phosphorylation. (5) Excess acetyl-CoA released by oxidation of fatty acids and not required by the liver is converted to the ketone bodies, acetoacetate and β-hydroxybutyrate; these circulate in the blood to other tissues, to be used as fuel for the citric acid cycle. Ketone bodies may be regarded as a transport form of acetyl groups. They can supply a significant fraction of the energy in some extrahepatic tissues—up to one-third in the heart, and as much as 60% to 70% in the brain during prolonged fasting. (6) Some of the acetyl-CoA derived from fatty acids (and from glucose) is used for the biosynthesis of cholesterol, which is required for membrane synthesis. Cholesterol is also the precursor of all steroid hormones and of the bile salts, which are essential for the digestion and absorption of lipids.

The final two metabolic fates of lipids involve specialized mechanisms for the transport of insoluble lipids in the blood. (7) Fatty acids are converted to the phospholipids and TAGs of plasma lipoproteins, which carry lipids to adipose tissue for storage as TAGs. (8) Some free fatty acids become bound to serum albumin and are carried to the heart and skeletal muscles, which absorb and oxidize free fatty acids as a major fuel. Serum albumin is the most abundant plasma protein; one molecule of serum albumin can carry up to 10 molecules of free fatty acid to the tissues where the fatty acids are released and consumed.

The liver thus serves as the body's distribution center, exporting nutrients in the correct proportions to other organs, smoothing out fluctuations in metabolism caused by intermittent food intake, and processing excess amino groups into urea and other products to be disposed of by the kidneys. Certain nutrients are stored in the liver, including Fe ions and vitamin A. The liver also detoxifies foreign organic compounds, such as drugs, food additives, preservatives, and other possibly harmful agents with no food value. Detoxification often involves the cytochrome P-450–dependent hydroxylation of relatively insoluble organic compounds, making them sufficiently soluble for further breakdown and excretion (see Box 21–1).

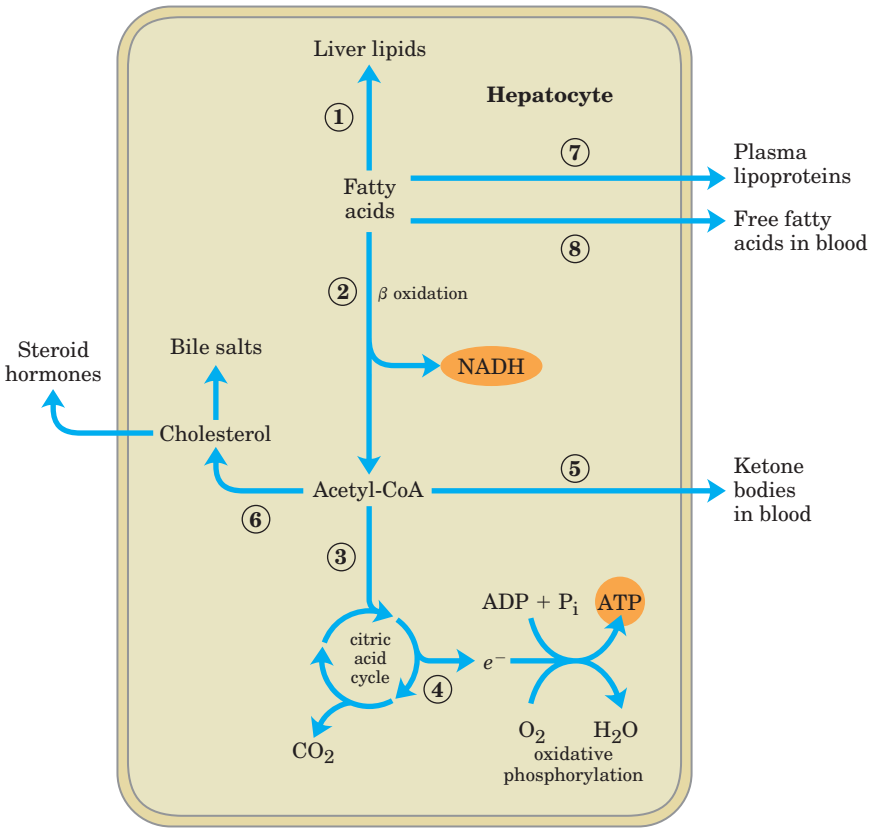


FIGURE 23–15 Metabolism of fatty acids in the liver.

Adipose Tissue Stores and Supplies Fatty Acids

Adipose tissue, which consists of **adipocytes** (fat cells) (Fig. 23–16), is amorphous and widely distributed in the body: under the skin, around the deep blood vessels, and in the abdominal cavity. It typically makes up about 15% of the mass of a young adult human, with approximately 65% of this mass in the form of triacylglycerols. Adipocytes are metabolically very active, responding quickly to hormonal stimuli in a metabolic interplay with the liver, skeletal muscles, and the heart.

Like other cell types, adipocytes have an active glycolytic metabolism, use the citric acid cycle to oxidize pyruvate and fatty acids, and carry out oxidative phosphorylation. During periods of high carbohydrate intake, adipose tissue can convert glucose (via pyruvate and acetyl-CoA) to fatty acids, convert the fatty acids to TAGs, and store them as large fat globules—although, in humans, much of the fatty acid synthesis occurs in hepatocytes. Adipocytes store TAGs arriving from the liver (carried in the blood as VLDLs; see Fig. 21–40a) and from the intestinal tract (carried in chylomicrons), particularly after meals rich in fat.

When fuel demand rises, lipases in adipocytes hydrolyze stored TAGs to release free fatty acids, which can travel in the bloodstream to skeletal muscles and the heart. The release of fatty acids from adipocytes is greatly accelerated by epinephrine, which stimulates the cAMP-dependent phosphorylation of perilipin; this gives triacylglycerol lipase access to TAGs in the lipid droplet. The hormone-sensitive lipase is also stimulated by phosphorylation, but this is not the main cause of increased lipolysis (see Fig. 17–3). Insulin counterbalances this effect of epinephrine, decreasing the activity of triacylglycerol lipase.

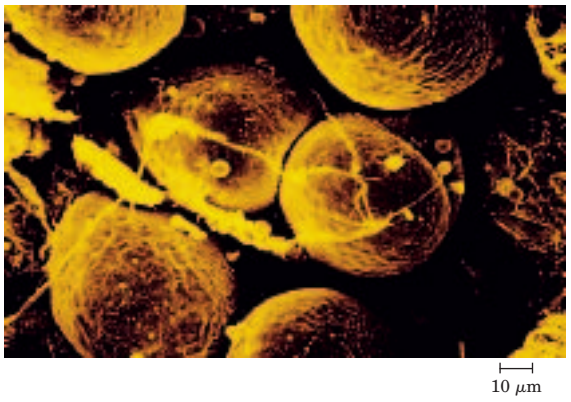


FIGURE 23–16 Scanning electron micrograph of human adipocytes. In fat tissues, capillaries and collagen fibers form a supporting network around spherical adipocytes. Almost the entire volume of these metabolically active cells is taken up by fat droplets.

The breakdown and synthesis of TAGs in adipose tissues constitute a substrate cycle; up to 70% of the fatty acids released by triacylglycerol lipase are reesterified in adipocytes, re-forming TAGs. Recall from Chapter 15 that such substrate cycles allow fine regulation of the rate and direction of flow of intermediates through a bidirectional pathway. In adipose tissue, glycerol liberated by triacylglycerol lipase cannot be reused in the synthesis of TAGs, because adipocytes lack the enzyme glycerol kinase. Instead, the glycerol phosphate required for TAG synthesis is made from pyruvate by glyceroneogenesis, involving the cytosolic enzyme PEP carboxykinase (see Fig. 21–22). This enzyme is one target of the drugs (thiazolidinediones) used in the treatment of type II diabetes, raising the possibility that defective regulation of cytosolic PEP carboxykinase in fat tissue may be a causative factor in type II diabetes.

Human infants, and many hibernating animals, have adipose tissue called brown fat, which is specialized to generate heat rather than ATP during oxidation of fatty acids. Adult humans have very little brown fat tissue.

Muscles Use ATP for Mechanical Work

Metabolism in the cells of skeletal muscle—the **myocytes**—is specialized to generate ATP as the immediate source of energy for contraction. Moreover, skeletal muscle is adapted to do its mechanical work in an intermittent fashion, on demand. Sometimes skeletal muscles must work at their maximum capacity for a short time, as in a 100 m sprint; at other times more prolonged work is required, as in running a marathon or extended physical labor.

There are two general classes of muscle tissue, which differ in physiological role and fuel utilization. **Slow-twitch muscle,** also called red muscle, provides relatively low tension but is highly resistant to fatigue. It produces ATP by the relatively slow but steady process of oxidative phosphorylation. Red muscle is very rich in mitochondria and is served by very dense networks of blood vessels, which bring the oxygen essential to ATP production. It is the cytochromes in mitochondria and the hemoglobin in blood that give the tissue its characteristic red color. **Fast-twitch muscle,** or white muscle, has fewer mitochondria than red muscle and is less well supplied with blood vessels, but it can develop greater tension, and do so faster. White muscle is quicker to fatigue, because when active, it uses ATP faster than it can replace it. There is a genetic component to the proportion of red and white muscle in any individual; with training, the endurance of fast-twitch muscle can be improved.

Skeletal muscle can use free fatty acids, ketone bodies, or glucose as fuel, depending on the degree of muscular activity (Fig. 23–17). In resting muscle, the primary fuels are free fatty acids from adipose tissue and

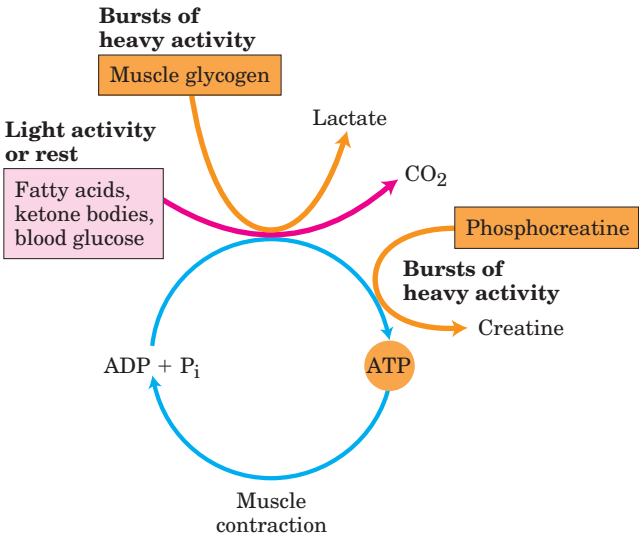


FIGURE 23–17 Energy sources for muscle contraction. Different fuels are used for ATP synthesis during bursts of heavy activity and during light activity or rest. Phosphocreatine can rapidly supply ATP.

ketone bodies from the liver. These are oxidized and degraded to yield acetyl-CoA, which enters the citric acid cycle for oxidation to CO_2. The ensuing transfer of electrons to O_2 provides the energy for ATP synthesis by oxidative phosphorylation. Moderately active muscle uses blood glucose in addition to fatty acids and ketone bodies. The glucose is phosphorylated, then degraded by glycolysis to pyruvate, which is converted to acetyl-CoA and oxidized via the citric acid cycle and oxidative phosphorylation.

In maximally active fast-twitch muscles, the demand for ATP is so great that the blood flow cannot provide O_2 and fuels fast enough to supply sufficient ATP by aerobic respiration alone. Under these conditions, stored muscle glycogen is broken down to lactate by fermentation (p. 523). Each glucose unit degraded yields three ATP, because phosphorolysis of glycogen produces glucose 6-phosphate, sparing the ATP normally consumed in the hexokinase reaction. Lactic acid fermentation thus responds to an increased need for ATP more quickly than does oxidative phosphorylation, supplementing basal ATP production that results from aerobic oxidation of other fuels via the citric acid cycle and respiratory chain. The use of blood glucose and muscle glycogen as fuels for muscular activity is greatly enhanced by the secretion of epinephrine, which stimulates both the release of glucose from liver glycogen and the breakdown of glycogen in muscle tissue.

The relatively small amount of glycogen in skeletal muscle (about 1% of its total weight) limits the amount of glycolytic energy available during all-out exertion. Moreover, the accumulation of lactate and consequent decrease in pH in maximally active muscles reduces their efficiency. Skeletal muscle, however, contains another

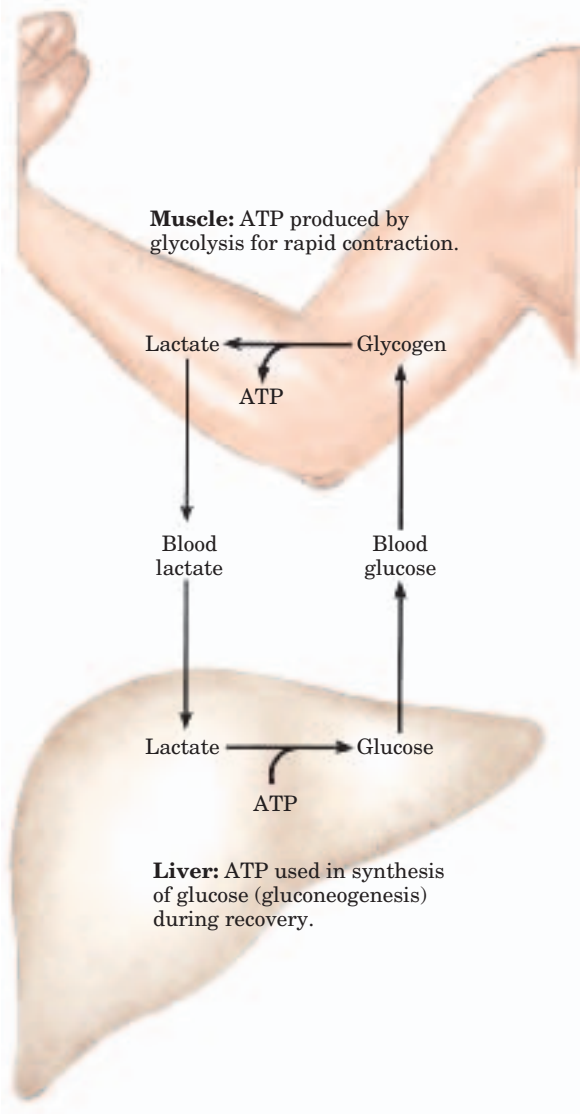
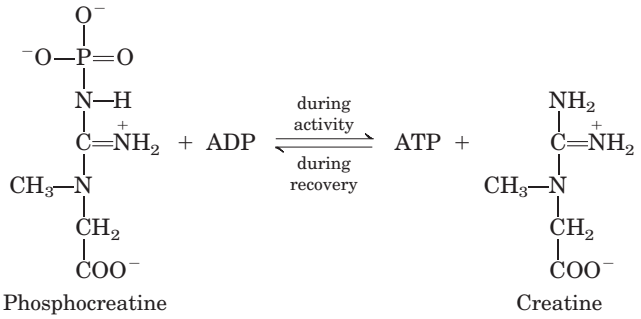


FIGURE 23–18 Metabolic cooperation between skeletal muscle and the liver. Extremely active muscles use glycogen as energy source, generating lactate via glycolysis. During recovery, some of this lactate is transported to the liver and converted to glucose via gluconeogenesis. This glucose is released to the blood and returned to the muscles to replenish their glycogen stores. The overall pathway (glucose → lactate → glucose) constitutes the Cori cycle.

source of ATP, in the form of phosphocreatine (10 to 30 mM), which can rapidly regenerate ATP from ADP by the creatine kinase reaction:



During periods of active contraction and glycolysis, this reaction proceeds predominantly in the direction of ATP synthesis; during recovery from exertion, the same enzyme resynthesizes phosphocreatine from creatine at the expense of ATP.

After a period of intense muscular activity, the individual continues breathing heavily for some time, using much of the extra O_2 for oxidative phosphorylation in the liver. The ATP produced is used for gluconeogenesis from lactate that has been carried in the blood from the muscles. The glucose thus formed returns to the muscles to replenish their glycogen, completing the Cori cycle (Fig. 23–18; see also Box 15–1).

Heart muscle differs from skeletal muscle in that it is continuously active in a regular rhythm of contraction and relaxation, and it has a completely aerobic metabolism at all times. Mitochondria are much more abundant in heart muscle than in skeletal muscle, making up almost half the volume of the cells (Fig. 23–19). The heart uses as its fuel mainly free fatty acids, but also some glucose and ketone bodies taken up from the blood; these fuels are oxidized via the citric acid cycle and oxidative phosphorylation to generate ATP. Like skeletal muscle, heart muscle does not store lipids or glycogen in large amounts. It does have small amounts of reserve energy in the form of phosphocreatine, enough for a few seconds of contraction. Because the heart is normally aerobic and obtains its energy from oxidative phosphorylation, the failure of O_2 to reach a portion of the heart muscle when the blood vessels are blocked by lipid deposits (atherosclerosis) or blood clots (coronary thrombosis) can cause that region of the heart muscle to die. This is what happens in myocardial infarction, more commonly known as a heart attack. ■

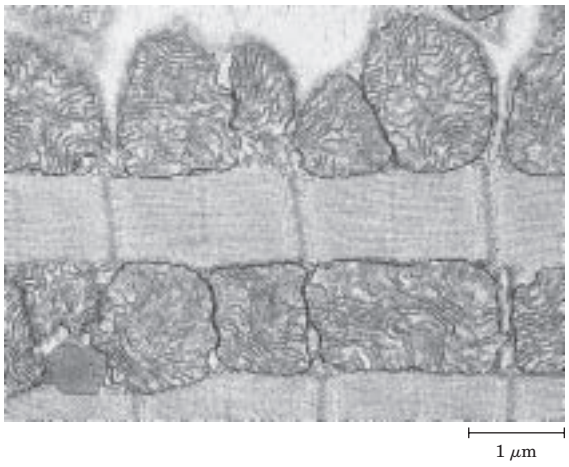


FIGURE 23–19 Electron micrograph of heart muscle. In the profuse mitochondria of heart tissue, pyruvate, fatty acids, and ketone bodies are oxidized to drive ATP synthesis. This steady aerobic metabolism allows the human heart to pump blood at a rate of nearly 6 L/min, or about 350 L/hr—or 200×10^6 L over 70 years.

The Brain Uses Energy for Transmission of Electrical Impulses

The metabolism of the brain is remarkable in several respects. The neurons of the adult mammalian brain normally use only glucose as fuel (Fig. 23–20). (Astrocytes, the other major cell type in the brain, can oxidize fatty acids.) The brain has a very active respiratory metabolism (Fig. 23–21); it uses O_2 at a fairly constant rate, accounting for almost 20% of the total O_2 consumed by the body at rest. Because the brain contains very little glycogen, it is constantly dependent on incoming glucose from the blood. Should blood glucose fall significantly below a critical level for even a short time, severe and sometimes irreversible changes in brain function may result.

Although the neurons of the brain cannot directly use free fatty acids or lipids from the blood as fuels, they can, when necessary, use β-hydroxybutyrate (a ketone body), which is formed from fatty acids in the liver. The capacity of the brain to oxidize β-hydroxybutyrate via acetyl-CoA becomes important during prolonged fasting or starvation, after liver glycogen has been depleted, because it allows the brain to use body fat as an energy source. This spares muscle proteins—until they become the brain's ultimate source of glucose (via gluconeogenesis in the liver) during severe starvation.

Neurons oxidize glucose by glycolysis and the citric acid cycle, and the flow of electrons from these oxidations through the respiratory chain provides almost all the ATP used by these cells. Energy is required to create and maintain an electrical potential across the neuronal plasma membrane. The membrane contains an electrogenic ATP-driven antiporter, the Na^+K^+ ATPase, which simultaneously pumps 2 K^+ ions into and 3 Na^+ ions out of the neuron (see Fig. 11–37). The resulting transmembrane potential changes transiently as an electrical signal (action potential) sweeps from one end of a neuron to the other (see Fig. 12–5). Action potentials are the chief mechanism of information transfer in the nervous system, so a depletion of ATP in neurons has disastrous effects on all activities coordinated by neuronal signaling.

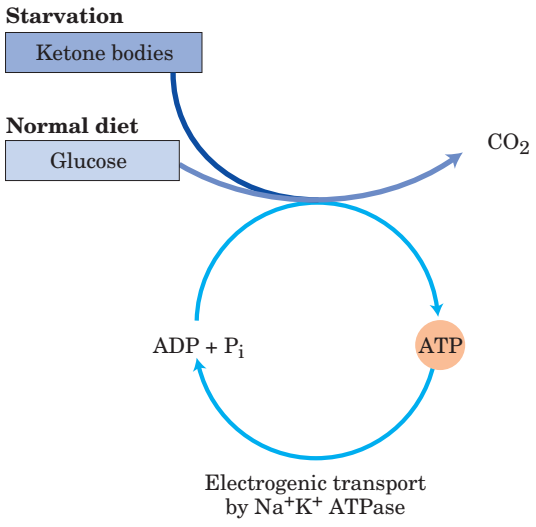


FIGURE 23–20 Energy sources in the brain vary with nutritional state. The ketone body used by the brain is β-hydroxybutyrate.

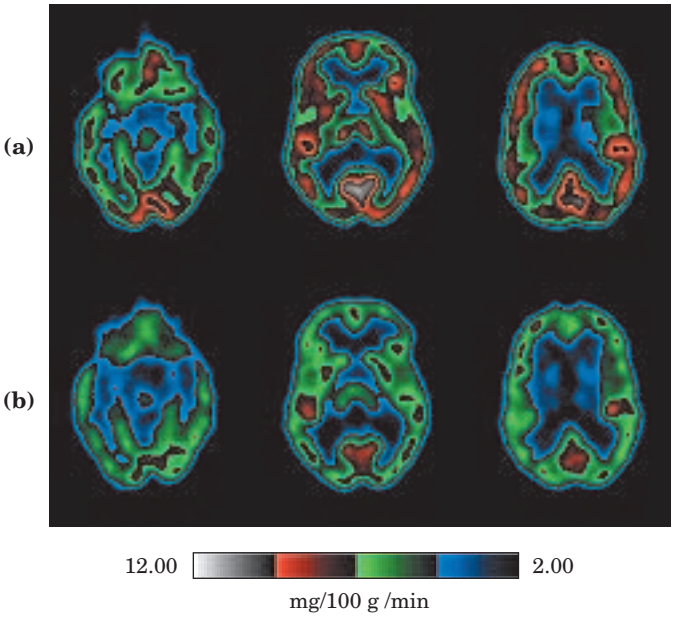


FIGURE 23–21 Glucose metabolism in the brain. The technique of positron emission tomography (PET) scanning shows metabolic activity in specific regions of the brain. PET scans allow visualization of isotopically labeled glucose in precisely localized regions of the brain of a living person, in real time. A positron-emitting glucose analog (2-[^{18}F]-fluoro-2-deoxy-D-glucose) is injected into the bloodstream; a few seconds later, a PET scan shows how much of the glucose has been taken up by each region of the brain—a measure of metabolic activity. Shown here are PET scans of front-to-back cross sections of the brain at three levels, from the top (at the left) downward (to the right). The scans compare glucose metabolism (in mg/100 g/min) when the experimental subject **(a)** is rested and **(b)** has been deprived of sleep for 48 hours.

Blood Carries Oxygen, Metabolites, and Hormones

Blood mediates the metabolic interactions among all tissues. It transports nutrients from the small intestine to the liver, and from the liver and adipose tissue to other organs; it also transports waste products from the tissues to the kidneys for excretion. Oxygen moves in the bloodstream from the lungs to the tissues, and CO_2 generated by tissue respiration returns via the bloodstream to the lungs for exhalation. Blood also carries hormonal signals from one tissue to another. In its role as signal carrier, the circulatory system resembles the nervous system; both regulate and integrate the activities of different organs.

The average adult human has 5 to 6 L of blood. Almost half of this volume is occupied by three types of blood cells (Fig. 23–22): **erythrocytes** (red cells), filled with hemoglobin and specialized for carrying O_2 and CO_2; much smaller numbers of **leukocytes** (white cells) of several types (including **lymphocytes**, also found in lymphatic tissue), which are central to the immune system that defends against infections; and **platelets,** which help to mediate blood clotting. The liquid portion is the **blood plasma,** which is 90% water and 10% solutes. Dissolved or suspended in the plasma is a large variety of proteins, lipoproteins, nutrients, metabolites, waste products, inorganic ions, and hormones. More than 70% of the plasma solids are **plasma proteins** (Fig. 23–22), primarily immunoglobulins (circulating antibodies), serum albumin, apolipoproteins involved in the transport of lipids, transferrin (for iron transport), and blood-clotting proteins such as fibrinogen and prothrombin.

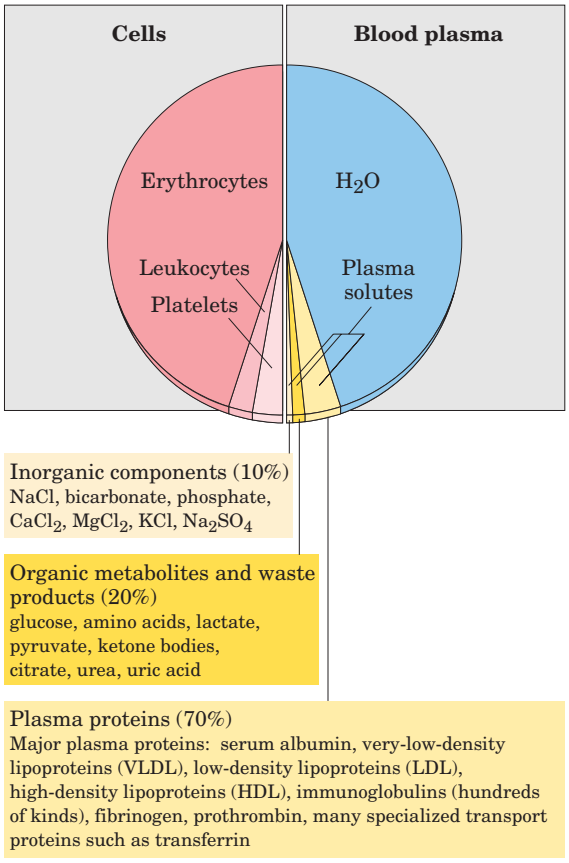


FIGURE 23–22 The composition of blood. Whole blood can be separated into blood plasma and cells by centrifugation. About 10% of blood plasma is solutes, of which about 10% consists of inorganic salts, 20% small organic molecules, and 70% plasma proteins. The major dissolved components are listed. Blood contains many other substances, often in trace amounts. These include other metabolites, enzymes, hormones, vitamins, trace elements, and bile pigments. Measurements of the concentrations of components in blood plasma are important in the diagnosis and treatment of many diseases.

The ions and low molecular weight solutes in blood plasma are not fixed components but are in constant flux between blood and various tissues. Dietary uptake of the inorganic ions that are the predominant electrolytes of blood and cytosol (Na^+, K^+, and Ca^{2+}) is, in general, counterbalanced by their excretion in the urine. For many blood components, something near a dynamic steady state is achieved; the concentration of the component changes little, although a continuous flux occurs between the digestive tract, blood, and urine. The plasma levels of Na^+, K^+, and Ca^{2+} remain close to 140, 5, and 2.5 mM, respectively, with little change in response to dietary intake. Any significant departure from these values can result in serious illness or death. The kidneys play an especially important role in maintaining ion balance by selectively filtering waste products and excess ions out of the blood while preventing the loss of essential nutrients and ions.

The concentration of glucose in the plasma is also subject to tight regulation. We have noted the constant requirement of the brain for glucose and the role of the liver in maintaining blood glucose in the normal range of 60 to 90 mg/100 mL. When blood glucose in a human drops to 40 mg/100 mL (the hypoglycemic condition), the person experiences discomfort and mental confusion (Fig. 23–23); further reductions lead to coma, convulsions, and in extreme hypoglycemia, death.

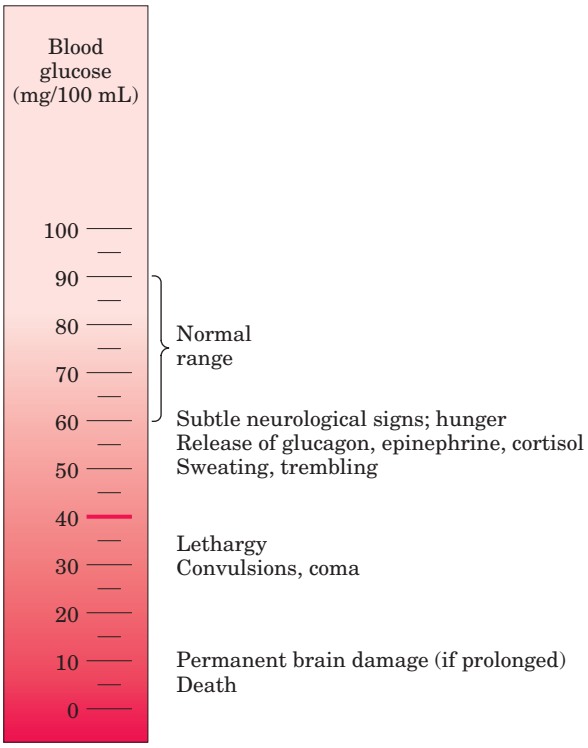


FIGURE 23–23 Physiological effects of low blood glucose in humans. Blood glucose levels of 40 mg/100 mL and below constitute severe hypoglycemia.

Maintaining the normal concentration of glucose in the blood is therefore a very high priority of the organism, and a variety of regulatory mechanisms have evolved to achieve that end. Among the most important regulators of blood glucose are the hormones insulin, glucagon, and epinephrine, as discussed in Section 23.3. ■

SUMMARY 23.2 Tissue-Specific Metabolism: The Division of Labor

- In mammals there is a division of metabolic labor among specialized tissues and organs. The liver is the central distributing and processing organ for nutrients. Sugars and amino acids produced in digestion cross the intestinal epithelium and enter the blood, which carries them to the liver. Some triacylglycerols derived from ingested lipids also make their way to the liver, where the constituent fatty acids are used in a variety of processes.
- Glucose 6-phosphate is the key intermediate in carbohydrate metabolism. It may be polymerized into glycogen, dephosphorylated to blood glucose, or converted to fatty acids via acetyl-CoA. It may undergo oxidation by glycolysis, the citric acid cycle, and respiratory chain to yield ATP, or enter the pentose phosphate pathway to yield pentoses and NADPH.
- Amino acids are used to synthesize liver and plasma proteins, or their carbon skeletons are converted to glucose and glycogen by gluconeogenesis; the ammonia formed by deamination is converted to urea.
- The liver converts fatty acids to triacylglycerols, phospholipids, or cholesterol and its esters, for transport as plasma lipoproteins to adipose tissue for storage. Fatty acids can also be oxidized to yield ATP or to form ketone bodies, which are circulated to other tissues.
- Skeletal muscle is specialized to produce and use ATP for mechanical work. During strenuous muscular activity, glycogen is the ultimate fuel, supplying ATP through lactic acid fermentation. During recovery, the lactate is reconverted (through gluconeogenesis) to glycogen and glucose in the liver. Phosphocreatine is an immediate source of ATP during active contraction.
- Heart muscle obtains nearly all its ATP from oxidative phosphorylation.
- The neurons of the brain use only glucose and β-hydroxybutyrate as fuels, the latter being important during fasting or starvation. The brain uses most of its ATP for the active transport of Na^+ and K^+ and maintenance of the electrical potential across the neuronal membrane.
- The blood carries nutrients, waste products, and hormonal signals among the organs.

23.3 Hormonal Regulation of Fuel Metabolism

The minute-by-minute adjustments that keep the blood glucose level near 4.5 mM involve the combined actions of insulin, glucagon, epinephrine, and cortisol on metabolic processes in many body tissues, but especially in liver, muscle, and adipose tissue. Insulin signals these tissues that blood glucose is higher than necessary; as a result, cells take up excess glucose from the blood and convert it to the storage compounds glycogen and triacylglycerol. Glucagon signals that blood glucose is too low, and tissues respond by producing glucose through glycogen breakdown and (in liver) gluconeogenesis and by oxidizing fats to reduce the use of glucose. Epinephrine is released into the blood to prepare the muscles, lungs, and heart for a burst of activity. Cortisol mediates the body's response to longer-term stresses. We discuss these hormonal regulations in the context of three normal metabolic states—well-fed, fasted, and starving—and look at the metabolic consequences of diabetes mellitus, which results from derangements in the signaling pathways that control glucose metabolism.

The Pancreas Secretes Insulin or Glucagon in Response to Changes in Blood Glucose

When glucose enters the bloodstream from the intestine after a carbohydrate-rich meal, the resulting increase in blood glucose causes increased secretion of **insulin** (and decreased secretion of glucagon). Insulin release by the pancreas is largely regulated by the level of glucose in the blood supplied to the pancreas. The peptide hormones insulin, glucagon, and somatostatin are produced by clusters of specialized pancreatic cells, the islets of Langerhans (Fig. 23–24). Each cell type of the islets produces a single hormone: α cells produce glucagon; β cells, insulin; and δ cells, somatostatin.

When blood glucose rises, GLUT2 transporters carry glucose into the β cells, where it is immediately converted to glucose 6-phosphate by hexokinase IV (glucokinase) and enters glycolysis (Fig. 23–25). The increased rate of glucose catabolism raises [ATP], causing the closing of ATP-gated K^+ channels in the plasma membrane. Reduced efflux of K^+ depolarizes the membrane, thereby opening voltage-sensitive Ca^{2+} channels in the plasma membrane. The resulting influx of Ca^{2+}

triggers the release of insulin by exocytosis. Stimuli from the parasympathetic and sympathetic nervous systems also stimulate and inhibit insulin release, respectively. A simple feedback loop limits hormone release: insulin lowers blood glucose by stimulating glucose uptake by the tissues; the reduced blood glucose is detected by the β cell as a diminished flux through the hexokinase reaction; this slows or stops the release of insulin. This feedback regulation holds blood glucose concentration nearly constant despite large fluctuations in dietary intake.

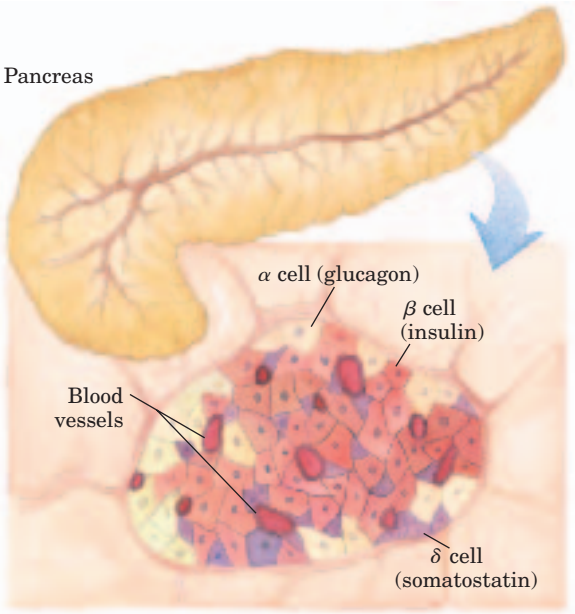


FIGURE 23–24 The endocrine system of the pancreas. In addition to the exocrine cells (see Fig. 18–3b), which secrete digestive enzymes in the form of zymogens, the pancreas contains endocrine tissue, the islets of Langerhans. The islets contain α, β, and δ cells (also known as A, B, and D cells, respectively), each cell type secreting a specific polypeptide hormone.

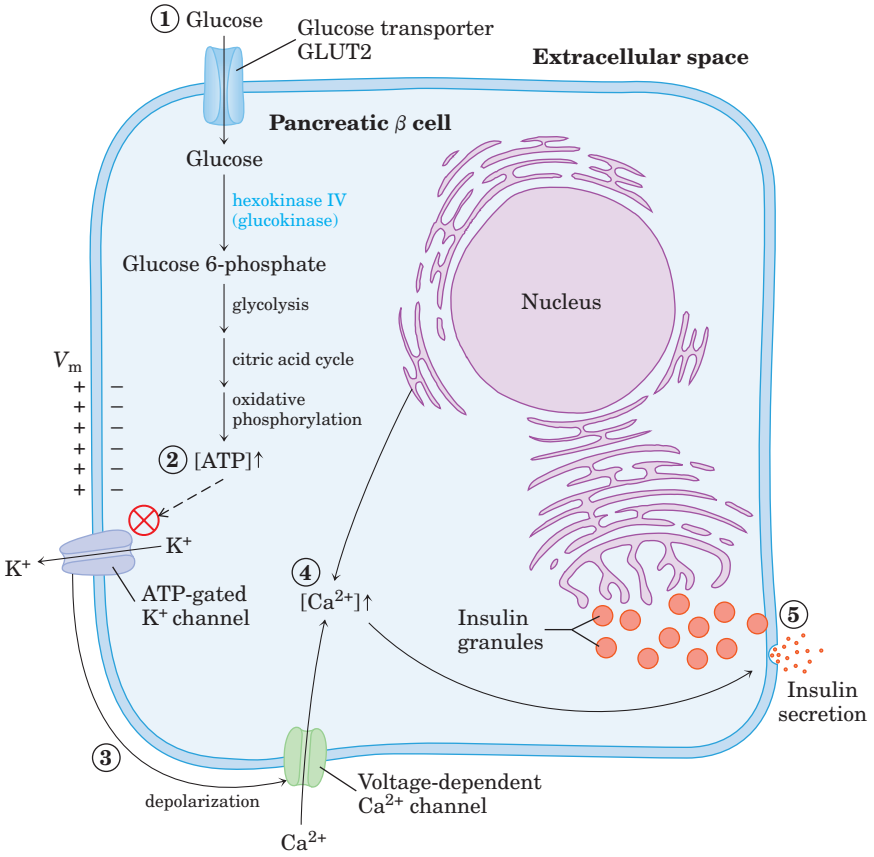


FIGURE 23–25 Glucose regulation of insulin secretion by pancreatic β cells. When the blood glucose level is high, active metabolism of glucose in the β cell raises intracellular [ATP], which leads to closing of K^+ channels in the plasma membrane, depolarizing the membrane. In response to the change in membrane potential, voltage-gated Ca^{2+} channels in the plasma membrane open, allowing Ca^{2+} to flow into the cell; this raises the cytosolic [Ca^{2+}] enough to trigger insulin release by exocytosis.

Insulin Counters High Blood Glucose

Insulin stimulates glucose uptake by muscle and adipose tissue (Table 23–3), where the glucose is converted to glucose 6-phosphate. In the liver, insulin also activates glycogen synthase and inactivates glycogen phosphorylase, so that much of the glucose 6-phosphate is channeled into glycogen.

Insulin also stimulates the storage of excess fuel as fat (Fig. 23–26). In the liver, insulin activates both the oxidation of glucose 6-phosphate to pyruvate via glycolysis and the oxidation of pyruvate to acetyl-CoA. If not oxidized further for energy production, this acetyl-CoA is used for fatty acid synthesis in the liver, and the fatty acids are exported as the TAGs of plasma lipoproteins (VLDLs) to the adipose tissue. Insulin stimulates TAG synthesis in adipocytes, from fatty acids released from the VLDL triacylglycerols. These fatty acids are ultimately derived from the excess glucose taken up from the blood by the liver. In summary, the effect of insulin is to favor the conversion of excess blood glucose to two storage forms: glycogen (in the liver and muscle) and triacylglycerols (in adipose tissue) (Table 23–3).

Glucagon Counters Low Blood Glucose

Several hours after the intake of dietary carbohydrate, blood glucose levels fall slightly because of the ongoing oxidation of glucose by the brain and other tissues. Lowered blood glucose triggers secretion of glucagon and decreases insulin release (Fig. 23–27).

Glucagon causes an increase in blood glucose concentration in several ways (Table 23–4). Like epinephrine, it stimulates the net breakdown of liver glycogen

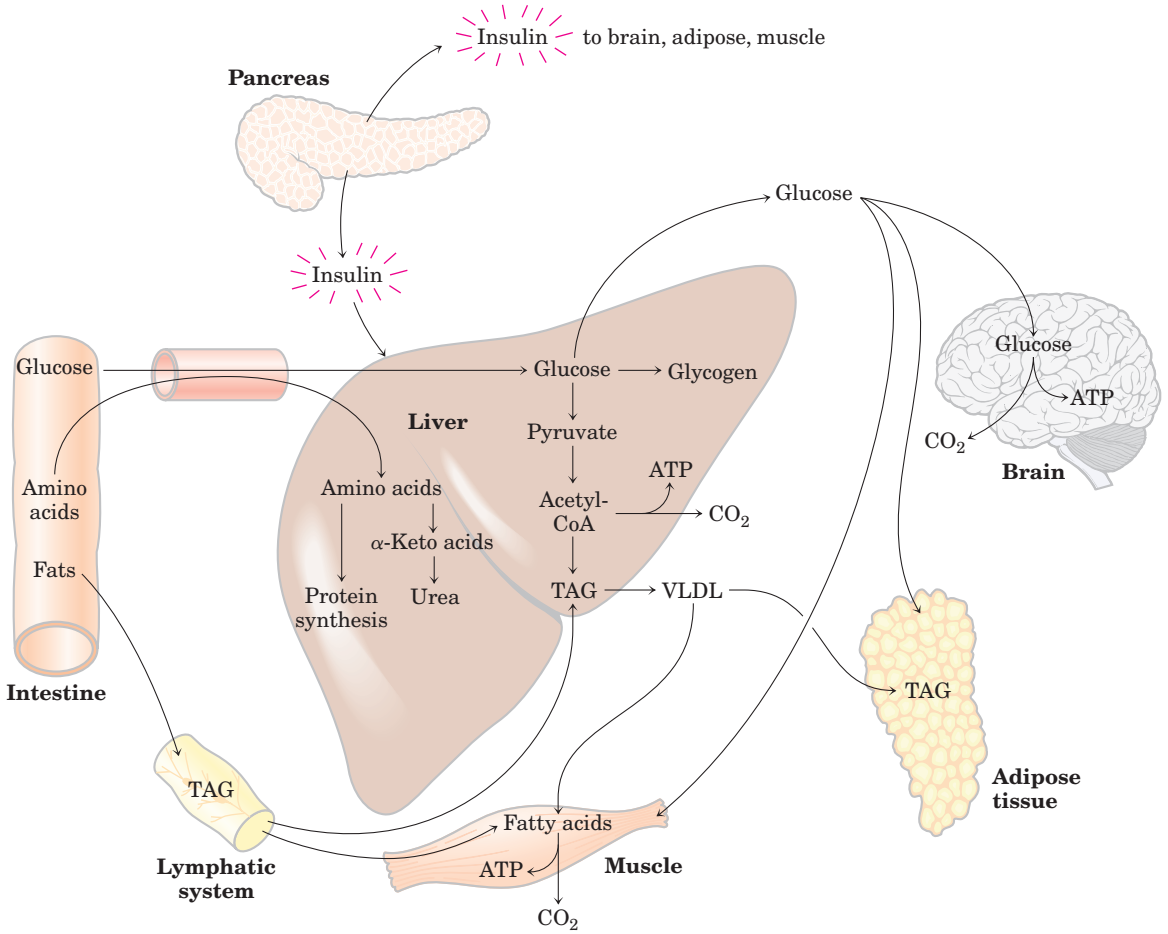


FIGURE 23–26 The well-fed state: the lipogenic liver. Immediately after a calorie-rich meal, glucose, fatty acids, and amino acids enter the liver. Insulin released in response to the high blood glucose concentration stimulates glucose uptake by the tissues. Some glucose is exported to the brain for its energetic needs, and some to fat and muscle tissue. In the liver, excess glucose is oxidized to acetyl-CoA, which is used to synthesize fatty acids for export as triacylglycerols in VLDLs to fat and muscle tissue. The NADPH necessary for lipid synthesis is obtained by oxidation of glucose in the pentose phosphate pathway. Excess amino acids are converted to pyruvate and acetyl-CoA, which are also used for lipid synthesis. Dietary fats move via the lymphatic system, as chylomicrons, from the intestine to muscle and fat tissues.

TABLE 23–3 Effects of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen

Metabolic effect	*Target enzyme*
↑ Glucose uptake (muscle, adipose)	↑ Glucose transporter (GLUT4)
↑ Glucose uptake (liver)	↑ Glucokinase (increased expression)
↑ Glycogen synthesis (liver, muscle)	↑ Glycogen synthase
↓ Glycogen breakdown (liver, muscle)	↓ Glycogen phosphorylase
↑ Glycolysis, acetyl-CoA production (liver, muscle)	↑ PFK-1 (by ↑ PFK-2)
	↑ Pyruvate dehydrogenase complex
↑ Fatty acid synthesis (liver)	↑ Acetyl-CoA carboxylase
↑ Triacylglycerol synthesis (adipose tissue)	↑ Lipoprotein lipase

by activating glycogen phosphorylase and inactivating glycogen synthase; both effects are the result of phosphorylation of the regulated enzymes, triggered by cAMP. Glucagon inhibits glucose breakdown by glycolysis in the liver and stimulates glucose synthesis by gluconeogenesis. Both effects result from lowering the concentration of fructose 2,6-bisphosphate, an allosteric inhibitor of the gluconeogenic enzyme fructose 1,6-bisphosphatase (FBPase-1) and an activator of phosphofructokinase-1. Recall that [fructose 2,6-bisphosphate] is ultimately controlled by a cAMP-dependent protein phosphorylation reaction (see Fig. 15–23). Glucagon also inhibits the glycolytic enzyme pyruvate kinase (by promoting its cAMP-dependent phosphorylation), thus blocking the conversion of phosphoenolpyruvate to pyruvate and preventing oxidation of pyruvate via the citric acid cycle. The resulting accumulation of phosphoenolpyruvate favors gluconeogenesis. This effect is augmented by glucagon's stimulation of the synthesis of the gluconeogenic enzyme PEP carboxykinase. By stimulating glycogen breakdown, preventing glycolysis, and promoting gluconeogenesis in hepatocytes, glucagon

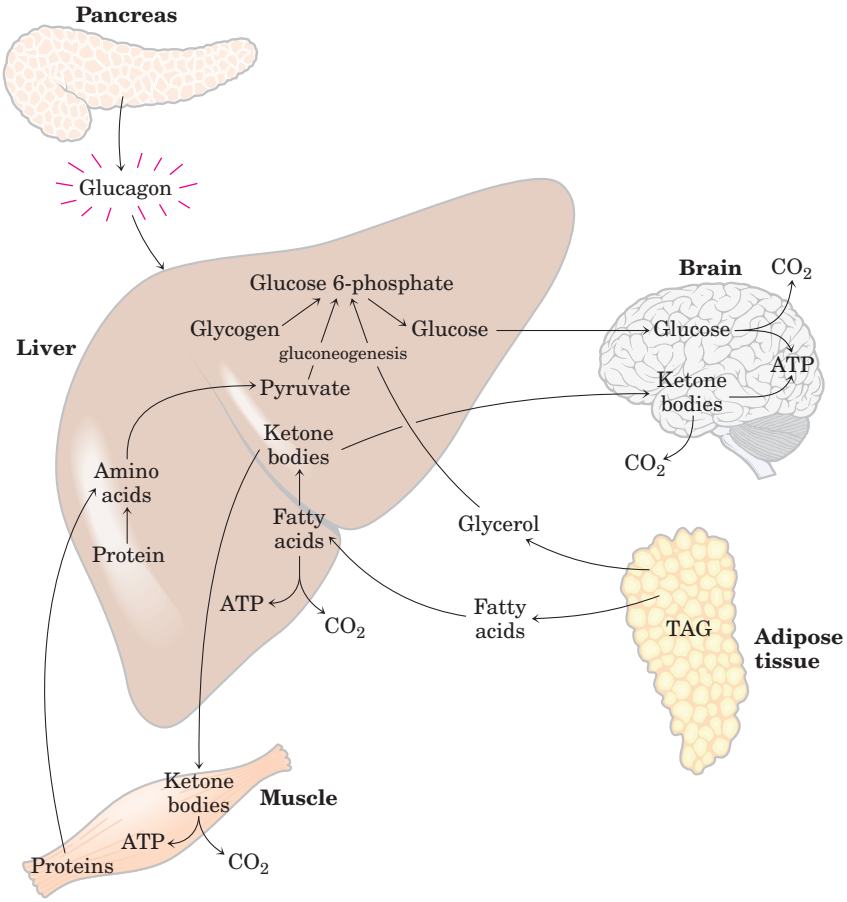


FIGURE 23–27 The fasting state: the glucogenic liver. After some hours without a meal, the liver becomes the principal source of glucose for the brain. Liver glycogen is broken down, and the glucose 1-phosphate produced is converted to glucose 6-phosphate, then to free glucose, which is released into the bloodstream. Amino acids from the degradation of proteins and glycerol from the breakdown of TAGs in adipose tissue are used for gluconeogenesis. The liver uses fatty acids as its principal fuel, and excess acetyl-CoA is converted to ketone bodies for export to other tissues for fuel; the brain is especially dependent on this fuel when glucose is in short supply.

TABLE 23–4 Effects of Glucagon on Blood Glucose: Production and Release of Glucose by the Liver

Metabolic effect	*Effect on glucose metabolism*	*Target enzyme*
↑ Glycogen breakdown (liver)	Glycogen ⟶ glucose	↑ Glycogen phosphorylase
↓ Glycogen synthesis (liver)	Less glucose stored as glycogen	↓ Glycogen synthase
↓ Glycolysis (liver)	Less glucose used as fuel in liver	↓ PFK-1
↑ Gluconeogenesis (liver)	Amino acids, Glycerol, Oxaloacetate ⟶ glucose	↑ FBPase-2 ↓ Pyruvate kinase ↑ PEP carboxykinase
↑ Fatty acid mobilization (adipose tissue)	Less glucose used as fuel by liver, muscle	↑ Triacylglycerol lipase Perilipin phosphorylation
↑ Ketogenesis	Provides alternative to glucose as energy source for brain	↑ Acetyl-CoA carboxylase

enables the liver to export glucose, restoring blood glucose to its normal level.

Although its primary target is the liver, glucagon (like epinephrine) also affects adipose tissue, activating TAG breakdown by causing cAMP-dependent phosphorylation of perilipin and triacylglycerol lipase. The activated lipase liberates free fatty acids, which are exported to the liver and other tissues as fuel, sparing glucose for the brain. The net effect of glucagon is therefore to stimulate glucose synthesis and release by the liver and to mobilize fatty acids from adipose tissue, to be used instead of glucose as fuel for tissues other than the brain (Table 23–4). All these effects of glucagon are mediated by cAMP-dependent protein phosphorylation.

During Fasting and Starvation, Metabolism Shifts to Provide Fuel for the Brain

The fuel reserves of a healthy adult human are of three types: glycogen stored in the liver and, in relatively small quantities, in muscles; large quantities of triacylglycerols in adipose tissues; and tissue proteins, which can be degraded when necessary to provide fuel (Table 23–5).

In the first few hours after a meal, the blood glucose level is diminished slightly, and tissues receive glucose released from liver glycogen. There is little or no synthesis of lipids. By 24 hours after a meal, blood glucose has fallen further, insulin secretion has slowed, and glucagon secretion has increased. These hormonal signals

TABLE 23–5 Available Metabolic Fuels in a Normal-Weight 70 kg Man and in an Obese 140 kg Man at the Beginning of a Fast

Type of fuel	*Weight (kg)*	*Caloric equivalent (thousands of kcal (kJ))*	*Estimated survival (months)**
Normal-weight, 70 kg man			
Triacylglycerols (adipose tissue)	15	141 (589)	
Proteins (mainly muscle)	6	24 (100)	
Glycogen (muscle, liver)	0.225	0.90 (3.8)	
Circulating fuels (glucose, fatty acids, triacylglycerols, etc.)	0.023	0.10 (0.42)	
Total		166 (694)	3
Obese, 140 kg man			
Triacylglycerols (adipose tissue)	80	752 (3,140)	
Proteins (mainly muscle)	8	32 (134)	
Glycogen (muscle, liver)	0.23	0.92 (3.8)	
Circulating fuels	0.025	0.11 (0.46)	
Total		785 (3,280)	14

*Survival time is calculated on the assumption of a basal energy expenditure of 1,800 kcal/day.

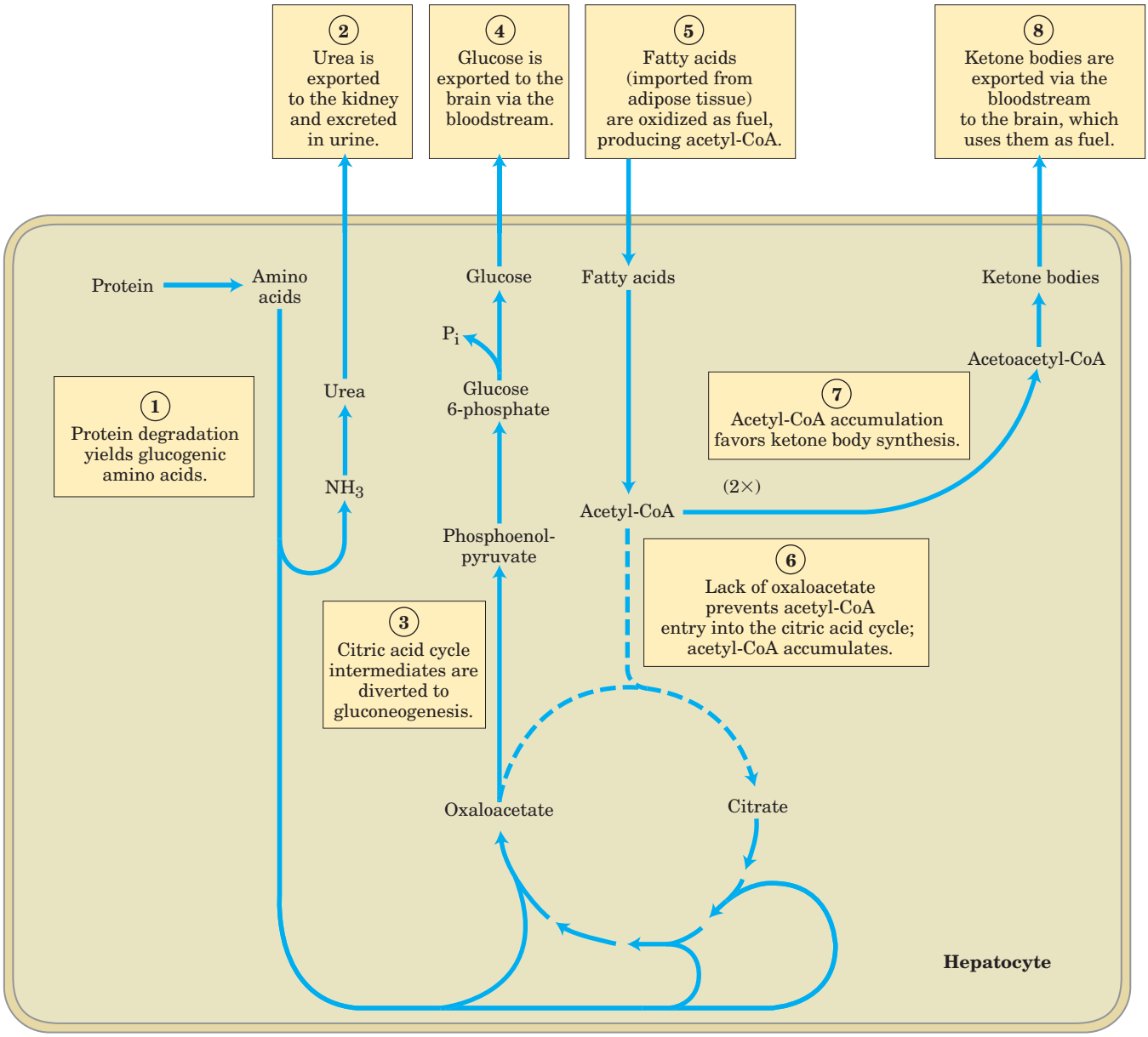


FIGURE 23–28 Fuel metabolism in the liver during prolonged fasting or in uncontrolled diabetes mellitus. After depletion of stored carbohydrates, ① to ④ proteins become an important source of glucose, produced from glucogenic amino acids by gluconeogenesis. ⑤ to ⑧ Fatty acids imported from adipose tissue are converted to ketone bodies for export to the brain. Broken arrows represent reactions with reduced flux under these conditions. The steps are further described in the text.

mobilize triacylglycerols, which now become the primary fuel for muscle and liver. Figure 23–28 shows the responses to prolonged fasting. ① To provide glucose for the brain, the liver degrades certain proteins—those most expendable in an organism not ingesting food. Their nonessential amino acids are transaminated or deaminated (Chapter 18), and ② the extra amino groups are converted to urea, which is exported via the bloodstream to the kidney and excreted.

Also in the liver, ③ the carbon skeletons of glucogenic amino acids are converted to pyruvate or intermediates of the citric acid cycle. ④ These intermediates, as well as the glycerol ⑤ derived from triacylglycerols in adipose tissue, provide the starting materials for gluconeogenesis in the liver, yielding glucose for the brain. Eventually the use of citric acid cycle intermediates for gluconeogenesis depletes oxaloacetate, inhibiting entry of acetyl-CoA into the citric acid cycle. ⑥ Acetyl-CoA produced by fatty acid oxidation now accumulates, favoring ⑦ the formation of acetoacetyl-CoA and ketone bodies in the liver. After a few days of fasting, the levels of ketone bodies in the blood rise (Fig.

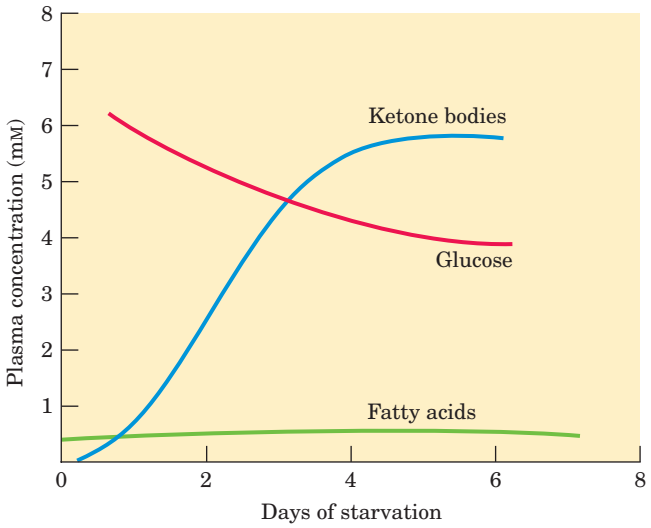


FIGURE 23–29 Concentrations of fatty acids, glucose, and ketone bodies in the plasma during the first week of starvation. Despite the hormonal mechanisms for maintaining the level of glucose in the blood, it begins to diminish after two days of fasting. The level of ketone bodies, almost immeasurable before the fast, rises dramatically after 2 to 4 days of fasting. These water-soluble ketones, acetoacetate and β-hydroxybutyrate, supplement glucose as an energy source during a long fast. Fatty acids cannot serve as a fuel for the brain; they do not cross the blood-brain barrier.

23–29) as these fuels are exported from the liver to the heart, skeletal muscle, and brain, which use them instead of glucose (⑧).

Acetyl-CoA is a critical regulator of the fate of pyruvate; it allosterically inhibits pyruvate dehydrogenase and stimulates pyruvate carboxylase (see Fig. 15–20). In these ways acetyl-CoA prevents it own further production from pyruvate while stimulating the conversion of pyruvate to oxaloacetate, the first step in gluconeogenesis.

Triacylglycerols stored in the adipose tissue of a normal-weight adult could provide enough fuel to maintain a basal rate of metabolism for about three months; a very obese adult has enough stored fuel to endure a fast of more than a year (Table 23–5). When fat reserves are gone, the degradation of essential proteins begins; this leads to loss of heart and liver function, and eventually death. Stored fat can provide adequate energy (calories) during a fast or rigid diet, but vitamins and minerals must be provided, and sufficient dietary glucogenic amino acids are needed to replace those being used for gluconeogenesis. Rations for those on a weight-reduction diet are therefore commonly fortified with vitamins, minerals, and amino acids or proteins.

Epinephrine Signals Impending Activity

When an animal is confronted with a stressful situation that requires increased activity—fighting or fleeing, in the extreme case—neuronal signals from the brain trigger the release of epinephrine and norepinephrine from the adrenal medulla. Both hormones dilate the respiratory passages to facilitate the uptake of O_2, increase the rate and strength of the heartbeat, and raise the blood pressure, thereby promoting the flow of O_2 and fuels to the tissues (Table 23–6).

Epinephrine acts primarily on muscle, adipose, and liver tissues. It activates glycogen phosphorylase and inactivates glycogen synthase by cAMP-dependent phosphorylation of the enzymes, thus stimulating the conversion of liver glycogen to blood glucose, the fuel for anaerobic muscular work. Epinephrine also promotes the anaerobic breakdown of muscle glycogen by lactic acid fermentation, stimulating glycolytic ATP formation. The stimulation of glycolysis is accomplished by raising the concentration of fructose 2,6-bisphosphate, a potent allosteric activator of the key glycolytic enzyme phosphofructokinase-1 (see Figs 15–22, 15–23). Epinephrine

TABLE 23–6 Physiological and Metabolic Effects of Epinephrine: Preparation for Action

Immediate effect	*Overall effect*
Physiological	
↑ Heart rate	Increase delivery of O_2 to tissues (muscle)
↑ Blood pressure	
↑ Dilation of respiratory passages	
Metabolic	
↑ Glycogen breakdown (muscle, liver)	Increase production of glucose for fuel
↓ Glycogen synthesis (muscle, liver)	
↑ Gluconeogenesis (liver)	
↑ Glycolysis (muscle)	Increases ATP production in muscle
↑ Fatty acid mobilization (adipose tissue)	Increases availability of fatty acids as fuel
↑ Glucagon secretion	Reinforce metabolic effects of epinephrine
↓ Insulin secretion	

also stimulates fat mobilization in adipose tissue, activating (by cAMP-dependent phosphorylation) both perilipin and triacylglycerol lipase (see Fig. 17–3). Finally, epinephrine stimulates glucagon secretion and inhibits insulin secretion, reinforcing its effect of mobilizing fuels and inhibiting fuel storage.

Cortisol Signals Stress, Including Low Blood Glucose

A variety of stressors (anxiety, fear, pain, hemorrhage, infections, low blood glucose, starvation) stimulate release of the corticosteroid hormone **cortisol** from the adrenal cortex. Cortisol acts on muscle, liver, and adipose tissue to supply the organism with fuel to withstand the stress. Cortisol is a relatively slow-acting hormone that alters metabolism by changing the kinds and amounts of certain enzymes synthesized in its target cell, rather than by regulating the activity of existing enzyme molecules.

In adipose tissue, cortisol leads to an increase in the release of fatty acids from stored TAGs. The fatty acids are exported to serve as fuel for other tissues, and the glycerol is used for gluconeogenesis in the liver. Cortisol stimulates the breakdown of muscle proteins and the export of amino acids to the liver, where they serve as precursors for gluconeogenesis. In the liver, cortisol promotes gluconeogenesis by stimulating synthesis of the key enzyme PEP carboxykinase (see Fig. 14–17b); glucagon has the same effect, whereas insulin has the opposite effect. Glucose produced in this way is stored in the liver as glycogen or exported immediately to tissues that need glucose for fuel. The net effect of these metabolic changes is to restore blood glucose to its normal level and to increase glycogen stores, ready to support the fight-or-flight response commonly associated with stress. The effects of cortisol therefore counterbalance those of insulin.

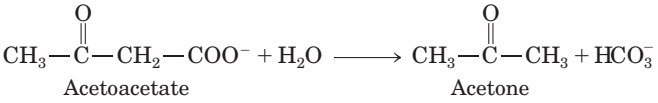
Diabetes Mellitus Arises from Defects in Insulin Production or Action

Diabetes mellitus, caused by a deficiency in the secretion or action of insulin, is a relatively common disease: nearly 6% of the United States population shows some degree of abnormality in glucose metabolism that is indicative of diabetes or a tendency toward the condition. There are two major clinical classes of diabetes mellitus: **type I diabetes,** or insulin-dependent diabetes mellitus (IDDM), and **type II diabetes,** or non-insulin-dependent diabetes mellitus (NIDDM), also called insulin-resistant diabetes.

In type I diabetes, the disease begins early in life and quickly becomes severe. This disease responds to insulin injection, because the metabolic defect stems from a paucity of pancreatic β cells and a consequent inability to produce sufficient insulin. IDDM requires insulin therapy and careful, lifelong control of the balance between dietary intake and insulin dose. Characteristic symptoms of type I (and type II) diabetes are excessive thirst and frequent urination (polyuria), leading to the intake of large volumes of water (polydipsia) ("diabetes mellitus" means "excessive excretion of sweet urine"). These symptoms are due to the excretion of large amounts of glucose in the urine, a condition known as **glucosuria.**

Type II diabetes is slow to develop (typically in older, obese individuals), and the symptoms are milder and often go unrecognized at first. This is really a group of diseases in which the regulatory activity of insulin is defective: insulin is produced, but some feature of the insulin-response system is defective. These individuals are insulin-resistant. The connection between type II diabetes and obesity (discussed below) is an active area of research.

Individuals with either type of diabetes are unable to take up glucose efficiently from the blood; recall that insulin triggers the movement of GLUT4 glucose transporters to the plasma membrane of muscle and adipose tissue (see Fig. 12–8). Another characteristic metabolic change in diabetes is excessive but incomplete oxidation of fatty acids in the liver. The acetyl-CoA produced by β oxidation cannot be completely oxidized by the citric acid cycle, because the high [NADH]/[NAD^+] ratio produced by β oxidation inhibits the cycle (recall that three steps convert NAD^+ to NADH). Accumulation of acetyl-CoA leads to overproduction of the ketone bodies acetoacetate and β-hydroxybutyrate, which cannot be used by extrahepatic tissues as fast as they are made in the liver. In addition to β-hydroxybutyrate and acetoacetate, the blood of diabetics also contains acetone, which results from the spontaneous decarboxylation of acetoacetate:



Acetone is volatile and is exhaled, and in uncontrolled diabetes, the breath has a characteristic odor sometimes mistaken for ethanol. A diabetic individual who is experiencing mental confusion due to high blood glucose is occasionally misdiagnosed as intoxicated, an error that can be fatal. The overproduction of ketone bodies, called **ketosis,** results in greatly increased concentrations of ketone bodies in the blood (ketonemia) and urine (ketonuria).

The ketone bodies are carboxylic acids, which ionize, releasing protons. In uncontrolled diabetes this acid production can overwhelm the capacity of the blood's bicarbonate buffering system and produce a lowering of blood pH called **acidosis** or, in combination with ketosis, **ketoacidosis,** a potentially life-threatening condition.

Biochemical measurements on blood and urine samples are essential in the diagnosis and treatment of diabetes. A sensitive diagnostic criterion is provided by

the **glucose-tolerance test.** The patient fasts overnight, then drinks a test dose of 100 g of glucose dissolved in a glass of water. The blood glucose concentration is measured before the test dose and at 30 min intervals for several hours thereafter. A healthy individual assimilates the glucose readily, the blood glucose rising to no more than about 9 or 10 mM; little or no glucose appears in the urine. Diabetic individuals assimilate the test dose of glucose poorly; their blood glucose level far exceeds the kidney threshold (about 10 mM), causing glucose to appear in the urine. ■

SUMMARY 23.3 Hormonal Regulation of Fuel Metabolism

- The concentration of glucose in blood is hormonally regulated. Fluctuations in blood glucose level (normally 60 to 90 mg/100 mL, or about 4.5 mM) due to dietary intake or vigorous exercise are counterbalanced by a variety of hormonally triggered changes in the metabolism of several organs.
- High blood glucose elicits the release of insulin, which speeds the uptake of glucose by tissues and favors the storage of fuels as glycogen and triacylglycerols, while inhibiting fatty acid mobilization in adipose tissue.
- Low blood glucose triggers release of glucagon, which stimulates glucose release from liver glycogen and shifts fuel metabolism in liver and muscle to fatty acid oxidation, sparing glucose for use by the brain. In prolonged fasting, triacylglycerols become the principal fuel; the liver converts the fatty acids to ketone bodies for export to other tissues, including the brain.
- Epinephrine prepares the body for increased activity by mobilizing blood glucose from glycogen and other precursors.
- Cortisol, released in response to a variety of stressors (including low blood glucose), stimulates gluconeogenesis from amino acids and glycerol in the liver, thus raising blood glucose and counterbalancing the effects of insulin.
- In diabetes, insulin is either not produced or not recognized by the tissues, and the uptake of blood glucose is compromised. When blood glucose levels are high, glucose is excreted. Tissues then depend on fatty acids for fuel (producing ketone bodies) and degrade cellular proteins to provide glucogenic amino acids for glucose synthesis. Uncontrolled diabetes is characterized by high glucose levels in the blood and urine and the production and excretion of ketone bodies.

23.4 Obesity and the Regulation of Body Mass

In the United States population, 30% of adults are obese and another 35% are overweight. (Obesity is defined in terms of body mass index (BMI): BMI = weight in kg/(height in m)^2. A BMI below 25 is considered normal; 25 to 30 is overweight, and greater than 30, obese.) Obesity is life-threatening. It significantly increases the chances of developing type II diabetes as well as heart attack, stroke, and cancers of the colon, breast, prostate, and endometrium. Consequently, there is great interest in understanding how body mass and the storage of fats in adipose tissue are regulated. ■

To a first approximation, obesity is the result of taking in more calories in the diet than are expended by the body's energy-consuming activities. The body can deal with an excess of dietary calories in three ways: (1) convert excess fuel to fat and store it in adipose tissue, (2) burn excess fuel by extra exercise, and (3) "waste" fuel by diverting it to heat production **(thermogenesis)** in uncoupled mitochondria. In mammals, a complex set of hormonal and neuronal signals act to keep fuel intake and energy expenditure in balance, so as to hold the amount of adipose tissue at a suitable level. Dealing effectively with obesity requires understanding these various checks and balances under normal conditions, and how these homeostatic mechanisms fail in obesity.

The Lipostat Theory Predicts the Feedback Regulation of Adipose Tissue

The **lipostat theory** postulates a mechanism that inhibits eating behavior and increases energy consumption whenever body weight exceeds a certain value (the set point); the inhibition is relieved when body weight drops below the set point (Fig. 23–30). This theory predicts that a feedback signal originating in adipose tissue influences the brain centers that control eating behavior and activity (metabolic and motor). The first such factor, leptin, was discovered in 1994, and several others are now known.

Leptin (Greek *leptos,* "thin") is a small protein (167 amino acids) that is produced in adipocytes and moves through the blood to the brain, where it acts on receptors in the hypothalamus to curtail appetite. Leptin was first identified as the product of a gene designated *OB* (obese) in laboratory mice. Mice with two defective copies of this gene (*ob/ob* genotype; lowercase letters signify a mutant form of the gene) show the behavior and physiology of animals in a constant state of starvation: their serum cortisol levels are elevated; they are unable to stay warm, they grow abnormally, do not reproduce, and exhibit unrestrained appetite. As a consequence of the last effect, they become severely obese,

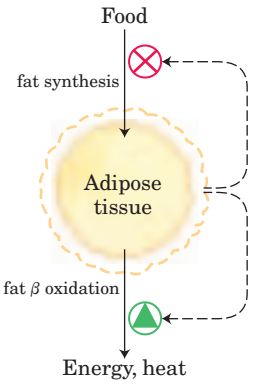


FIGURE 23–30 Set-point model for maintaining constant mass. When the mass of adipose tissue increases, released leptin inhibits feeding and fat synthesis and stimulates oxidation of fatty acids. When the mass of adipose tissue decreases, a lowered leptin production favors a greater food intake and less fatty acid oxidation.

weighing as much as three times more than normal mice (Fig. 23–31). They also have metabolic disturbances very similar to those of diabetic animals, and they are insulin-resistant. When leptin is injected into *ob/ob* mice, they lose weight and increase their locomotor activity and thermogenesis.

A second mouse gene, designated *DB* (diabetic), has also been found to have a role in appetite regulation. Mice with two defective copies (*db/db*) are obese and diabetic. The *DB* gene encodes the **leptin receptor.** When the leptin receptor is defective, the signaling function of leptin is lost.

The leptin receptor is expressed primarily in regions of the brain known to regulate feeding behavior—neurons of the arcuate nucleus of the hypothalamus (Fig. 23–32a). Leptin carries the message that fat reserves are sufficient, and it promotes a reduction in fuel intake and increased expenditure of energy. Leptin-receptor interaction in the hypothalamus alters the release of neuronal signals to the region of the brain that affects appetite. Leptin also stimulates the sympathetic nervous system, increasing blood pressure, heart rate, and thermogenesis by uncoupling electron transfer from ATP synthesis in the mitochondria of adipocytes (Fig. 23–32b). Recall that **thermogenin,** also called uncoupling protein (UCP), forms a channel in the inner mitochondrial membrane that allows protons to reenter the mitochondrial matrix without passing through the ATP synthase complex (see Fig. 19–30). This permits continual oxidation of fuel (fatty acids in an adipocyte) without ATP synthesis, dissipating energy as heat and consuming dietary calories or stored fats in potentially very large amounts.

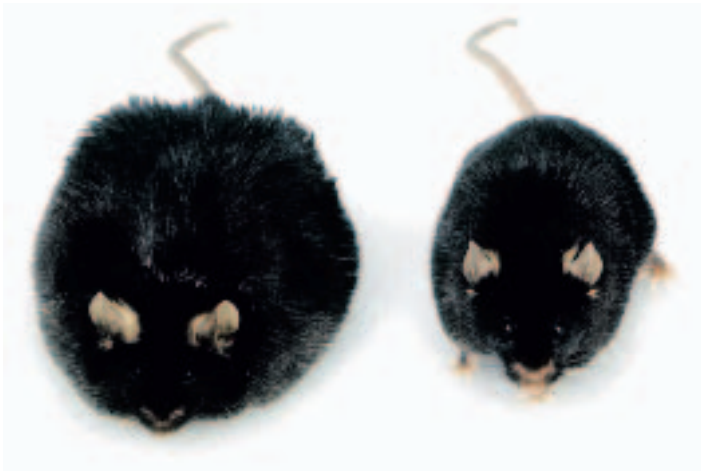


FIGURE 23–31 Obesity caused by defective leptin production. Both these mice, which are the same age, have defects in the *OB* gene. The mouse on the right was provided with purified leptin by daily injection, and weighs 35 g. The mouse on the left got no leptin, consequently ate more food and was less active, and weighs 67 g.

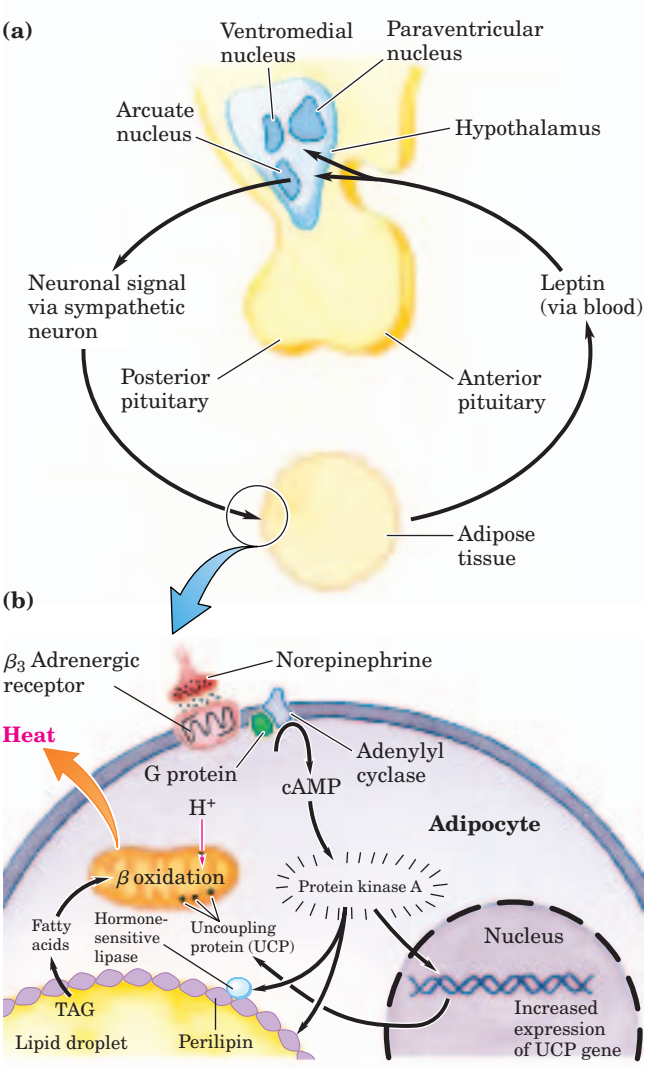


FIGURE 23–32 Hypothalamic regulation of food intake and energy expenditure. (a) Anatomy of the hypothalamus. **(b)** Interactions between the hypothalamus and an adipocyte, described later in text.

Leptin Stimulates Production of Anorexigenic Peptide Hormones

Two types of neurons in the arcuate nucleus control fuel intake and metabolism (Fig. 23–33). The **orexigenic** (appetite-stimulating) neurons stimulate eating by producing and releasing **neuropeptide Y (NPY),** which causes the next neuron in the circuit to send the signal to the brain, Eat! The blood level of NPY rises during starvation, and is elevated in both *ob/ob* and *db/db* mice. The high NPY concentration presumably underlies the obesity of these mice, who eat voraciously.

The **anorexigenic** (appetite-suppressing) neurons in the arcuate nucleus produce α-melanocyte-stimulating hormone **(α-MSH),** formed from its polypeptide precursor pro-opiomelanocortin (POMC; Fig. 23–6). Release of **α-MSH** causes the next neuron in the circuit to send the signal to the brain, Stop eating!

The amount of leptin released by adipose tissue depends on both the number and the size of adipocytes. When weight loss decreases the mass of lipid tissue, leptin levels in the blood decrease, the production of NPY is diminished, and the processes in adipose tissue shown in Figure 23–32 are reversed. Uncoupling is diminished,

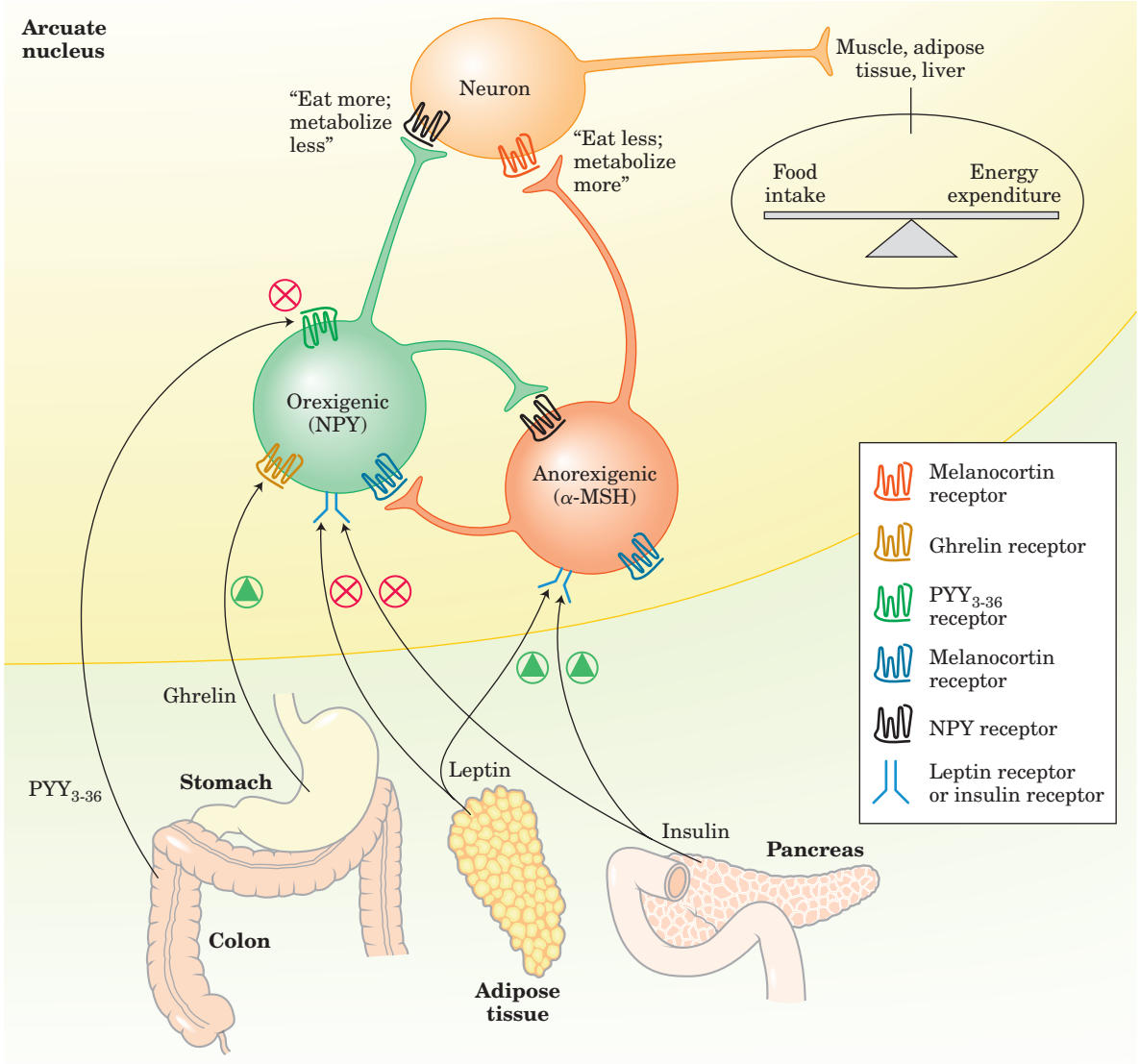


FIGURE 23–33 Hormones that control eating. In the arcuate nucleus, two sets of neurosecretory cells receive hormonal input and relay neuronal signals to the cells of muscle, adipose tissue, and liver. Leptin and insulin are released from adipose tissue and pancreas, respectively, in proportion to the mass of body fat. The two hormones act on anorexigenic neurosecretory cells (red) to trigger release of α-MSH; this produces neuronal signals to eat less and metabolize more fuel. Leptin and insulin also act on orexigenic neurosecretory cells (green) to inhibit the release of NPY, reducing the "eat" signal sent to the tissues. As described later in the text, the gastric hormone ghrelin *stimulates* appetite by activating the NPY-expressing cells; $PYY_{3–36}$, released from the colon, *inhibits* these neurons and thereby decreases appetite. Each of the two types of neurosecretory cells inhibits hormone production by the other, so any stimulus that activates orexigenic cells inactivates anorexigenic cells, and vice versa. This strengthens the effect of stimulatory inputs.

slowing thermogenesis and saving fuel, and fat mobilization slows in response to reduced signaling by cAMP. Consumption of more food combined with more efficient utilization of fuel results in replenishment of the fat reserve in adipose, bringing the system back into balance.

Leptin Triggers a Signaling Cascade That Regulates Gene Expression

The leptin signal is transduced by a mechanism also used by receptors for interferon and growth factors, the JAK-STAT system (Fig. 23–34; see Fig. 12–9). The leptin receptor, which has a single transmembrane segment, dimerizes when leptin binds to the extracellular domain of two monomers. Both monomers are phosphorylated on a Tyr residue of the intracellular domain by a ***Ja*nus *k*inase (JAK).** The Ⓟ–Tyr residues become docking sites for three proteins that are *s*ignal *t*ransducers and *a*ctivators of *t*ranscription (**STATs** 3, 5, and 6, sometimes called fat-STATS). The docked STATs are then phosphorylated on Tyr residues by the same JAK. After phosphorylation, the STATs dimerize then move to the nucleus, where they bind to specific DNA sequences and stimulate the expression of target genes, including the gene for POMC, from which α-MSH is produced.

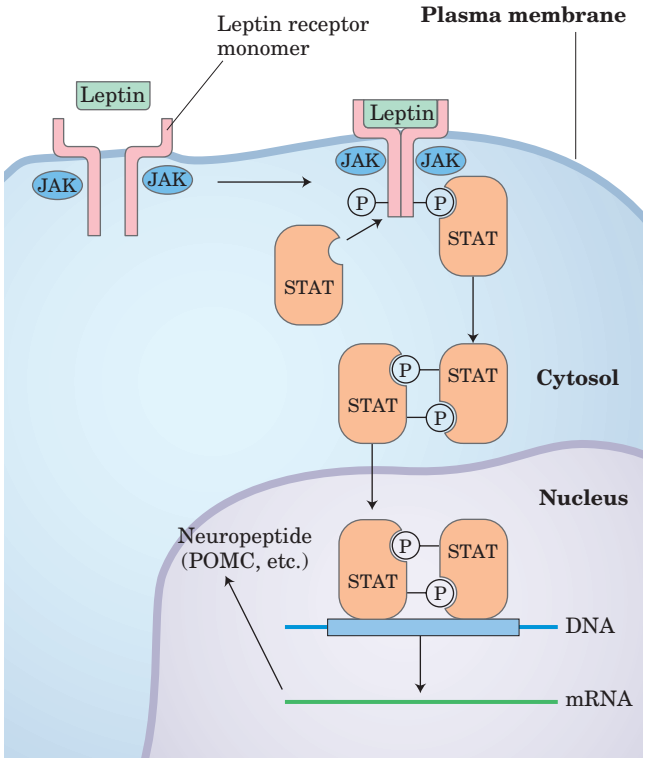


FIGURE 23–34 The JAK-STAT mechanism of leptin signal transduction in the hypothalamus. Leptin binding induces dimerization of the leptin receptor, followed by phosphorylation of Tyr residues of the receptor, catalyzed by Janus kinase (JAK). STATs bound to the phosphorylated leptin receptor through their SH2 domains are now phosphorylated on Tyr residues by a separate activity of JAK. The STATs dimerize, binding each other's Ⓟ–Tyr residues, and enter the nucleus. Here, they bind specific regulatory regions in the DNA and alter the expression of certain genes. The products of these genes ultimately influence the organism's feeding behavior and energy expenditure.

The increased catabolism and thermogenesis triggered by leptin are due in part to increased synthesis of the mitochondrial uncoupling protein UCP in adipocytes. Leptin stimulates the synthesis of this uncoupling protein by altering synaptic transmissions from neurons in the arcuate nucleus to adipose and other tissues. In these tissues, leptin causes increased release of norepinephrine, which acts through β_3-adrenergic receptors to stimulate transcription of the gene for UCP. The resulting uncoupling of electron transfer from oxidative phosphorylation consumes fat and is **thermogenic** (Fig. 23–32).

Might human obesity be the result of insufficient leptin production, and therefore treatable by the injection of leptin? Blood levels of leptin are in fact usually much *higher* in obese animals (including humans) than in animals of normal body mass (except, of course, in *ob/ob* animals, which cannot make leptin). Some downstream element in the leptin response system must be defective in obese individuals, and the elevation in leptin is the result of an (unsuccessful) attempt to overcome the leptin resistance. In those very rare humans with extreme obesity who have a defective leptin gene (*OB*), leptin injection does result in dramatic weight loss. In the vast majority of obese individuals, however, the *OB* gene is intact. In clinical trials, the injection of leptin did not have the weight-reducing effect observed in obese *ob/ob* mice. Clearly, most cases of human obesity involve one or more factors in addition to leptin.

The Leptin System May Have Evolved to Regulate the Starvation Response

Although much of the initial interest in leptin resulted from its possible role in preventing obesity, the leptin system probably evolved to adjust an animal's activity and metabolism during periods of fasting and starvation, not to restrict weight. The *reduction* in leptin level triggered by nutritional deficiency reverses the thermogenic processes illustrated in Figure 23–32, allowing fuel conservation. Leptin activates **AMP-dependent protein kinase (AMPK),** which regulates many aspects of fuel metabolism. Leptin also triggers decreased production of thyroid hormone (slowing basal metabolism), decreased production of sex hormones (preventing reproduction), and increased production of glucocorticoids (mobilizing the body's fuel-generating resources). By minimizing energy expenditures and maximizing the use of endogenous reserves of energy, these leptin-mediated responses may allow an animal to survive periods of severe nutritional deprivation.

Insulin Acts in the Arcuate Nucleus to Regulate Eating and Energy Conservation

Insulin secretion reflects both the size of fat reserves (adiposity) and the current energy balance (blood glucose level). Insulin acts on insulin receptors in the hypothalamus to inhibit eating (Fig. 23–33). Insulin receptors in the orexigenic neurons of the arcuate nucleus *inhibit* the release of NPY, and insulin receptors in the anorexigenic neurons *stimulate* α-MSH production, thereby decreasing fuel intake and increasing thermogenesis. By mechanisms discussed in Section 23.3, insulin also signals muscle, liver, and adipose tissues to increase catabolic reactions, including fat oxidation, which results in weight loss.

Leptin makes the cells of liver and muscle more sensitive to insulin. One hypothesis to explain this effect suggests cross-talk between the protein tyrosine kinases activated by leptin and those activated by insulin (Fig. 23–35); common second messengers in the two signaling pathways allow leptin to trigger some of the same downstream events that are triggered by insulin, through insulin receptor substrate-2 (IRS-2) and phosphoinositide 3-kinase (PI-3K) (Chapter 12).

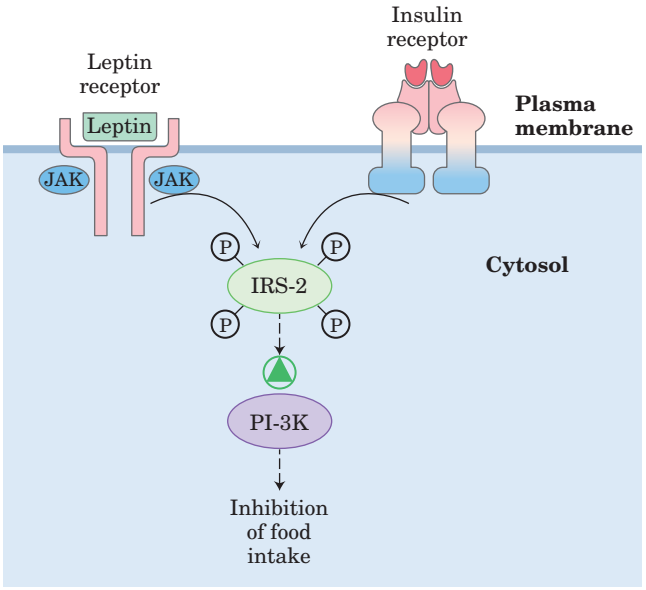


FIGURE 23–35 A possible mechanism for cross-talk between receptors for insulin and leptin. The insulin receptor has intrinsic Tyr kinase activity (see Fig. 12–6), and the leptin receptor, when occupied by its ligand, is phosphorylated by a soluble Tyr kinase (JAK). One possible explanation for the observed interaction between leptin and insulin is that both may phosphorylate the same substrate—in the case shown here, insulin receptor substrate-2 (IRS-2). When phosphorylated, IRS-2 activates PI-3K, which has downstream consequences that include inhibition of food intake. IRS-2 serves here as an integrator of the input from two receptors.

Adiponectin Acts through AMPK

Adiponectin is a peptide hormone (224 amino acids) produced almost exclusively in adipose tissue. It circulates in the blood and powerfully affects the metabolism of fatty acids and carbohydrates in liver and muscle. Adiponectin increases the uptake of fatty acids from the blood by myocytes and the rate at which fatty acids undergo β oxidation in the muscle. It also blocks fatty acid synthesis and gluconeogenesis in hepatocytes, and it stimulates glucose uptake and catabolism in muscle and liver (Fig. 23–36). These effects of adiponectin occur indirectly, through activation of the key regulatory enzyme AMPK by increased cytosolic [AMP]. Increased [AMP] also results from ATP consumption during intense muscular activity, but it can be brought about by adiponectin through other, unknown mechanisms. When activated, AMPK phosphorylates a number of target proteins critical to the metabolism of fatty acids and carbohydrates, with profound effects on the metabolism of the whole animal.

One enzyme regulated by AMPK is acetyl-CoA carboxylase, which produces malonyl-CoA, the first intermediate committed to fatty acid synthesis. Malonyl-CoA is a powerful inhibitor of the enzyme carnitine acyltransferase I, which starts the process of β oxidation by transporting fatty acids into the mitochondrion (see Fig. 17–6). By phosphorylating and inactivating acetyl-CoA carboxylase, AMPK inhibits fatty acid synthesis while relieving the inhibition (by malonyl-CoA) of β oxidation (Fig. 23–37).

Mice with defective adiponectin genes are less sensitive to insulin than those with normal adiponectin, and they show poor glucose tolerance; ingestion of dietary carbohydrate causes a long-lasting rise in their blood glucose. These metabolic defects resemble those of

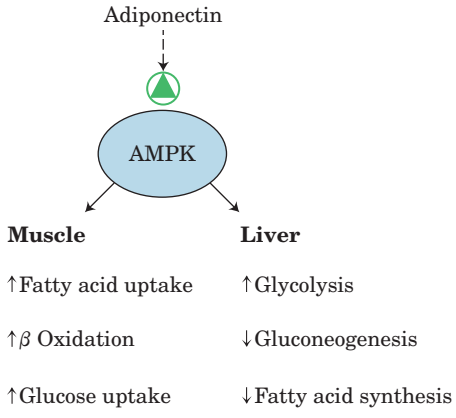


FIGURE 23–36 Effects of adiponectin on muscle and adipose tissue. By interacting with its receptors on the surface of myocytes and hepatocytes, adiponectin activates their AMPK. The activated kinase phosphorylates key metabolic enzymes (see Fig. 23–37, for example), shifting metabolism toward oxidation of fatty acids and away from lipid and glucose synthesis.

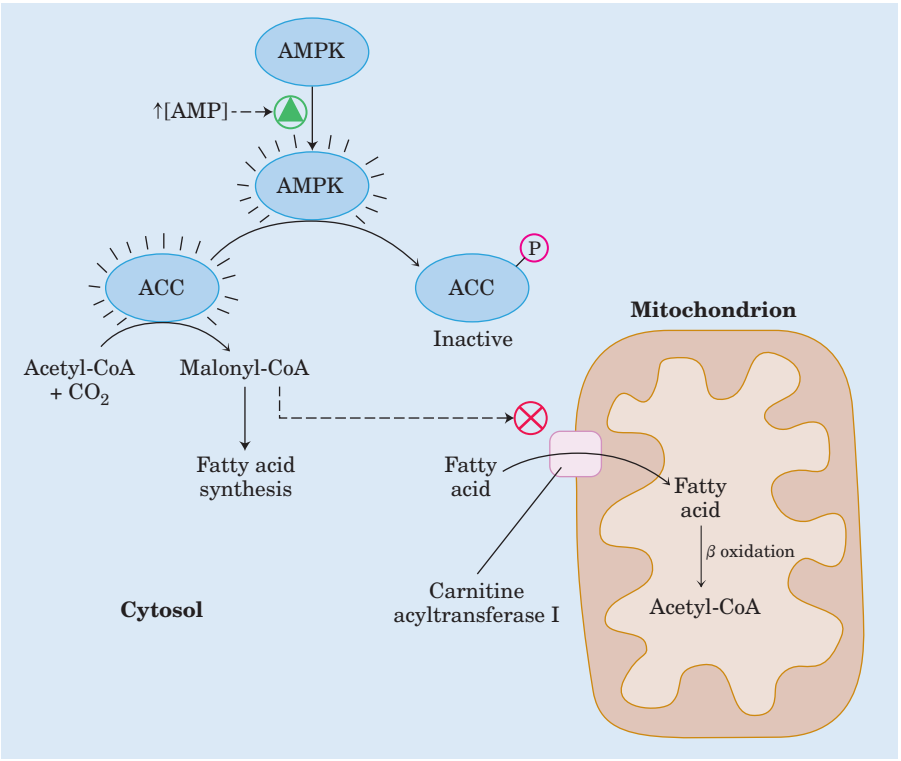


FIGURE 23–37 Regulation of fatty acid synthesis and β oxidation by AMPK action on acetyl-CoA carboxylase. When activated by elevated 5′-AMP, AMPK phosphorylates a Thr residue on acetyl-CoA carboxylase (ACC), inactivating it. This prevents the synthesis of malonyl-CoA, the first intermediate in fatty acid synthesis, and reduction in [malonyl-CoA] relieves the inhibition of carnitine acyltransferase I, allowing fatty acids to enter the mitochondrial matrix to undergo β oxidation.

humans with type II diabetes, who also are **insulin-insensitive** and clear glucose from the blood only slowly. Indeed, individuals with obesity or type II diabetes have lower blood adiponectin levels than nondiabetic controls. Moreover, the drugs used in treatment of type II diabetes—the thiazolidinediones, such as rosiglitazone (Avandia) and pioglitazone (Actos) (p. 807)—increase the expression of adiponectin mRNA in adipose tissue and increase blood adiponectin levels in experimental animals; they also activate AMPK. It appears that adiponectin, acting through AMPK, modulates the sensitivity of cells and tissues to insulin. Perhaps this hormone will prove to be one of the links between type II diabetes and its most important predisposing factor, obesity.

Three factors improve the health of individuals with type II diabetes: regular exercise, use of thiazolidinediones, and dietary restriction. We have seen that exercise activates AMPK, as does adiponectin, and that thiazolidinediones increase the concentration of adiponectin in plasma, increasing insulin sensitivity. Dietary restriction may act by regulating the expression of genes that encode proteins involved in fatty acid oxidation and in energy expenditure via thermogenesis.

Diet Regulates the Expression of Genes Central to Maintaining Body Mass

Proteins in a family of ligand-activated transcription factors, the **peroxisome proliferator-activated receptors (PPARs)**, respond to changes in dietary lipid by altering the expression of genes involved in fat and carbohydrate metabolism. These transcription factors were first recognized for their roles in peroxisome synthesis—thus their name. Their normal ligands are fatty acids or fatty acid derivatives, but they can also bind synthetic agonists and can be activated in the laboratory by genetic manipulation. PPARα, PPARδ, and PPARγ are members of the nuclear receptor superfamily. They act in the nucleus by forming heterodimers with another nuclear receptor, RXR (retinoid X receptor), binding to regulatory regions of DNA near the genes under their control and changing the rate of transcription of those genes (Fig. 23–38).

PPARγ, expressed primarily in liver and adipose tissue, is involved in turning on genes necessary to the differentiation of fibroblasts into adipocytes and genes that encode proteins required for lipid synthesis and storage in adipocytes. PPARγ is activated by drugs of the thiazolidinedione class, which are used to treat type II diabetes. **PPARα** in hepatocytes turns on the genes necessary for β oxidation of fatty acids and formation of ketone bodies during fasting.

PPARδ is a key regulator of fat oxidation, which acts by sensing changes in dietary lipid. It acts in liver and muscle, stimulating the transcription of at least nine genes encoding proteins for β oxidation and for energy dissipation through uncoupling of mitochondria. Normal mice overfed on high-fat diets accumulate massive amounts of both brown and white fat, and fat droplets accumulate in the liver. But when the same overfeeding experiment is done with mice that have a genetically

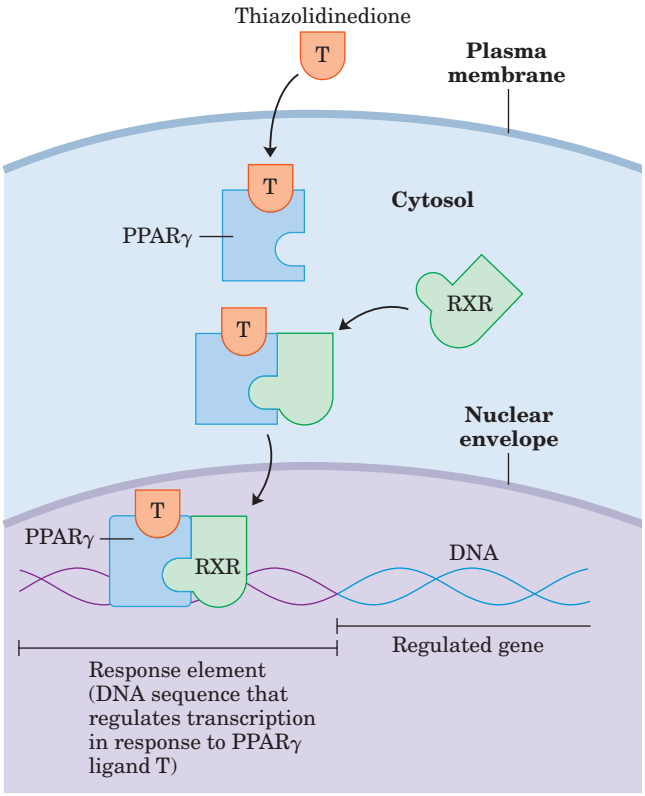


FIGURE 23–38 Mode of action of PPARs. PPARs, when bound to their cognate ligand, form heterodimers with the nuclear receptor RXR. The dimer binds specific regions of DNA, response elements, stimulating transcription of genes in those regions.

altered, always active PPARδ, this fat accumulation is prevented. In mice with a nonfunctioning leptin receptor (*db/db*), activated PPARδ prevents the development of obesity that would otherwise occur (see Fig. 23–31). By stimulating fatty acid breakdown in uncoupled mitochondria, PPARδ causes fat depletion, weight loss, and thermogenesis. Seen in this light, thermogenesis is both a means of keeping warm and a defense against obesity. Clearly, PPARδ is a potential target for drugs to treat obesity.

Short-Term Eating Behavior Is Set by Ghrelin and $PYY_{3–36}$

Ghrelin is a peptide hormone (28 amino acids) produced in cells lining the stomach. It was originally recognized as the stimulus for the release of growth hormone (*ghre* is the Proto-Indo-European root of "grow"), then subsequently shown to be a powerful appetite stimulant that works on a shorter time scale (between meals) than leptin and insulin. Ghrelin receptors are located in the pituitary gland (presumably mediating growth hormone release) and in the hypothalamus (affecting appetite), as well as in heart muscle and adipose tissue. The concentration of ghrelin in the blood varies strikingly between meals, peaking just before a meal and dropping sharply just after the meal (Fig. 23–39). Injection of ghrelin into humans produces immediate sensations of intense hunger. Individuals with Prader-Willi syndrome, whose blood levels of ghrelin are exceptionally high, have an uncontrollable appetite, leading to extreme obesity that often results in death before the age of 30.

$PYY_{3–36}$ is a peptide hormone (34 amino acids) secreted by endocrine cells in the lining of the small intestine and colon in response to food entering from the stomach. The level of $PYY_{3–36}$ in the blood rises after a meal and remains high for some hours. It is carried in the blood to the arcuate nucleus, where it acts on orexigenic neurons, inhibiting NPY release and reducing hunger (Fig. 23–33). Humans injected with $PYY_{3–36}$ feel little hunger and eat less than normal amounts for about 12 hours.

This interlocking system of neuroendocrine controls of food intake and metabolism presumably evolved to protect against starvation and to eliminate counterproductive accumulation of fat (extreme obesity). The difficulty most people face in trying to lose weight testifies to the remarkable effectiveness of these controls.

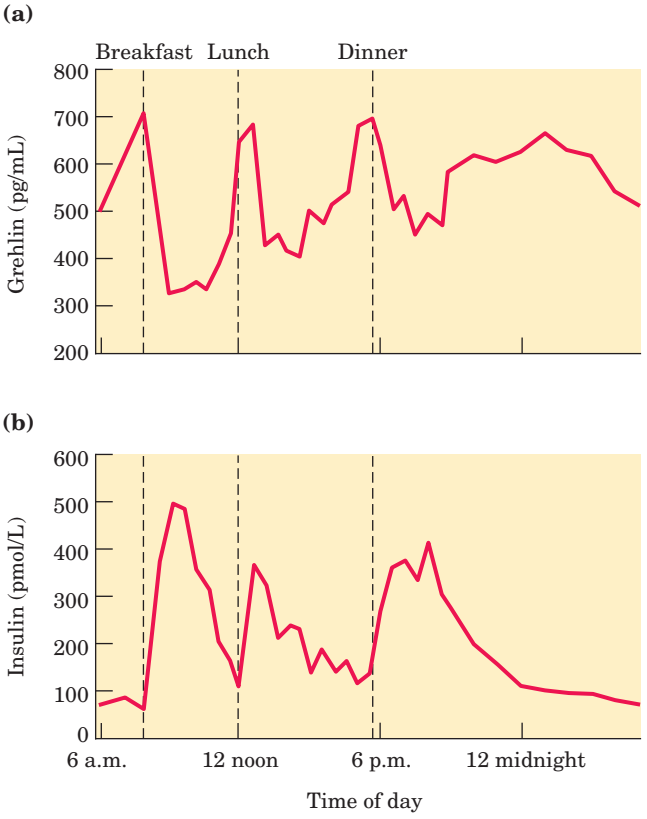


FIGURE 23–39 Variations in ghrelin and insulin relative to meal times. (a) Plasma levels of ghrelin rise sharply just *before* the normal time for meals (7 a.m. breakfast, 12 noon lunch, 5:30 p.m. dinner) and drop precipitously just after meals, paralleling the subjective feelings of hunger. **(b)** Insulin levels rise immediately *after* each meal, in response to the increase in blood glucose concentration.

SUMMARY 23.4 Obesity and the Regulation of Body Mass

- Obesity is increasingly common in the developed countries and predisposes people toward several life-threatening conditions.
- Adipose tissue produces leptin, a hormone that regulates feeding behavior and energy expenditure so as to maintain adequate reserves of fat. Leptin production and release increase with the number and size of adipocytes.
- Leptin acts on receptors in the arcuate nucleus of the hypothalamus, causing the release of anorexigenic peptides, including α-MSH, that act in the brain to inhibit eating. Leptin also stimulates sympathetic nervous system action on adipocytes, leading to uncoupling of mitochondrial oxidative phosphorylation, with consequent thermogenesis.
- The signal-transduction mechanism for leptin involves phosphorylation of the JAK-STAT system. On phosphorylation by JAK, STATs can bind to regulatory regions in nuclear DNA and alter the expression of genes for the proteins that set the level of metabolic activity and determine feeding behavior. Insulin acts on receptors in the arcuate nucleus, with results similar to those caused by leptin.
- The hormone adiponectin stimulates fatty acid uptake and oxidation and inhibits fatty acid synthesis. Its actions are mediated by AMPK.
- Ghrelin, a hormone produced in the stomach, acts on orexigenic neurons in the arcuate nucleus to produce hunger before a meal. $PYY_{3–36}$, a peptide hormone of the intestine, acts at the same site to lessen hunger after a meal.

Key Terms

Terms in bold are defined in the glossary.

neuroendocrine system 882
radioimmunoassay (RIA) 884
Scatchard analysis 884
endocrine glands 886
paracrine 886
autocrine 886
insulin 887
epinephrine 888
norepinephrine 888
catecholamines 888
eicosanoid hormones 888
steroid hormones 888
vitamin D hormone 889
retinoid hormones 889
thyroid hormones 889
nitric oxide (NO) 889
NO synthase 889
hypothalamus 889
posterior pituitary 890
anterior pituitary 890
tropic hormone 890
tropin 890
hepatocyte 893
adipocyte 897
myocyte 898
erythrocyte 901
leukocyte 901
lymphocyte 901
platelets 901
blood plasma 901
plasma proteins 901
cortisol 909
diabetes mellitus 909
type I diabetes 909
type II diabetes 909
glucosuria 909
ketosis 909
acidosis 909
ketoacidosis 909
glucose-tolerance test 910
thermogenesis 910
leptin 910
thermogenin (uncoupling protein) 911
orexigenic 912
neuropeptide Y (NPY) 912
anorexigenic 912
α-melanocyte-stimulating hormone (α-MSH) 912
Janus kinase (JAK) 913
STAT (signal transducer and activator of transcription) 913
thermogenic 913
AMP-dependent protein kinase (AMPK) 913
adiponectin 914
PPAR (peroxisome proliferator-activated receptor) 915
ghrelin 916
$PYY_{3–36}$ 916

Further Reading

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Problems

1. ATP and Phosphocreatine as Sources of Energy for Muscle During muscle contraction, the concentration of phosphocreatine in skeletal muscle drops while the concentration of ATP remains fairly constant. However, in a classic experiment, Robert Davies found that if he first treated muscle with 1-fluoro-2,4-dinitrobenzene (p. 97), the concentration of ATP declined rapidly while the concentration of phosphocreatine remained unchanged during a series of contractions. Suggest an explanation.

2. Metabolism of Glutamate in the Brain Brain tissue takes up glutamate from the blood, transforms it into glutamine, then releases it into the blood. What is accomplished by this metabolic conversion? How does it take place? The amount of glutamine produced in the brain can actually exceed the amount of glutamate entering from the blood. How does this extra glutamine arise? (Hint: You may want to review amino acid catabolism in Chapter 18; recall that NH_4^+ is very toxic to the brain.)

3. Absence of Glycerol Kinase in Adipose Tissue Glycerol 3-phosphate is required for the biosynthesis of triacylglycerols. Adipocytes, specialized for the synthesis and degradation of triacylglycerols, cannot use glycerol directly, because they lack glycerol kinase, which catalyzes the reaction

$$\text{Glycerol} + \text{ATP} \longrightarrow \text{glycerol 3-phosphate} + \text{ADP}$$

How does adipose tissue obtain the glycerol 3-phosphate necessary for triacylglycerol synthesis?

4. Oxygen Consumption during Exercise A sedentary adult consumes about 0.05 L of O_2 in 10 seconds. A sprinter, running a 100 m race, consumes about 1 L of O_2 in 10 seconds. After finishing the race, the sprinter continues to breathe at an elevated (but declining) rate for some minutes, consuming an extra 4 L of O_2 above the amount consumed by the sedentary individual.

(a) Why does the need for O_2 increase dramatically during the sprint?

(b) Why does the demand for O_2 remain high after the sprint is completed?

5. Thiamine Deficiency and Brain Function Individuals with thiamine deficiency show some characteristic neurological signs and symptoms, including loss of reflexes, anxiety, and mental confusion. Why might thiamine deficiency be manifested by changes in brain function?

6. Potency of Hormones Under normal conditions, the human adrenal medulla secretes epinephrine ($C_9H_{13}NO_3$) at a rate sufficient to maintain a concentration of 10^{-10} M in circulating blood. To appreciate what that concentration means, calculate the diameter of a round swimming pool, with a water depth of 2.0 m, that would be needed to dissolve 1.0 g (about 1 teaspoon) of epinephrine to a concentration equal to that in blood.

7. Regulation of Hormone Levels in the Blood The half-life of most hormones in the blood is relatively short. For example, when radioactively labeled insulin is injected into an animal, half of the labeled hormone disappears from the blood within 30 min.

(a) What is the importance of the relatively rapid inactivation of circulating hormones?

(b) In view of this rapid inactivation, how is the level of circulating hormone kept constant under normal conditions?

(c) In what ways can the organism make rapid changes in the level of a circulating hormone?

8. Water-Soluble versus Lipid-Soluble Hormones On the basis of their physical properties, hormones fall into one of two categories: those that are very soluble in water but relatively insoluble in lipids (e.g., epinephrine) and those that are relatively insoluble in water but highly soluble in lipids (e.g., steroid hormones). In their role as regulators of cellular activity, most water-soluble hormones do not enter their target cells. The lipid-soluble hormones, by contrast, do enter their target cells and ultimately act in the nucleus. What is the correlation between solubility, the location of receptors, and the mode of action of these two classes of hormones?

9. Metabolic Differences between Muscle and Liver in a "Fight or Flight" Situation During a "fight or flight" situation, the release of epinephrine promotes glycogen breakdown in the liver, heart, and skeletal muscle. The end product of glycogen breakdown in the liver is glucose; the end product in skeletal muscle is pyruvate.

(a) What is the reason for the different products of glycogen breakdown in the two tissues?

(b) What is the advantage to an organism that must fight or flee of these specific glycogen breakdown routes?

10. Excessive Amounts of Insulin Secretion: Hyperinsulinism Certain malignant tumors of the pancreas cause excessive production of insulin by the β cells. Affected individuals exhibit shaking and trembling, weakness and fatigue, sweating, and hunger.

(a) What is the effect of hyperinsulinism on the metabolism of carbohydrates, amino acids, and lipids by the liver?

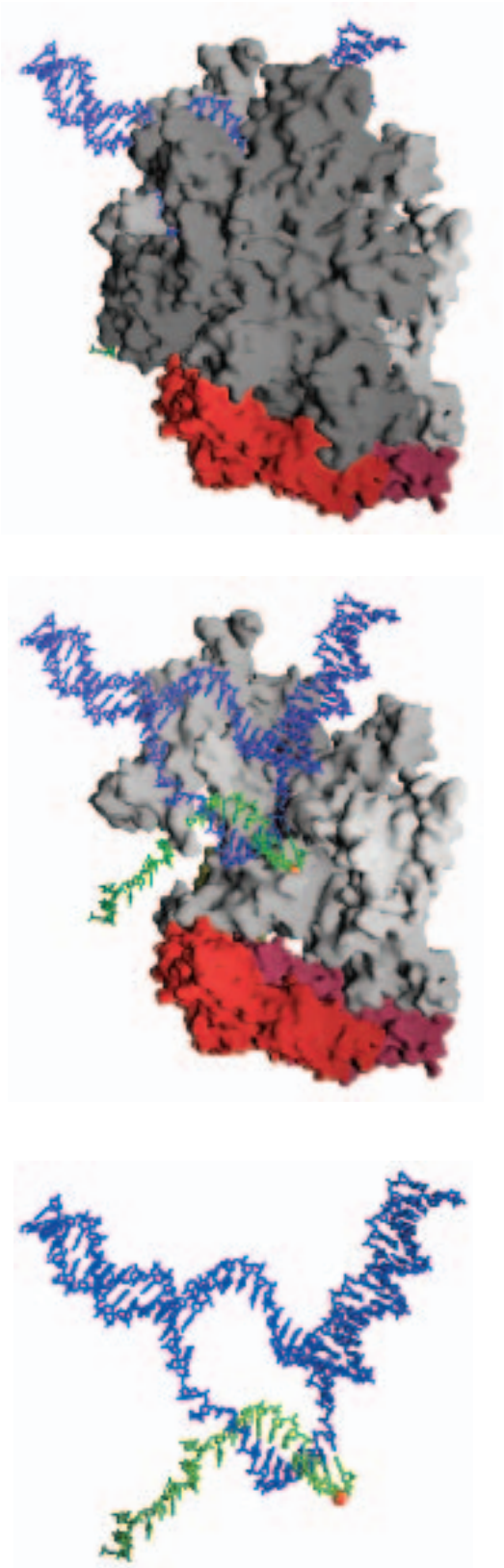
(b) What are the causes of the observed symptoms? Suggest why this condition, if prolonged, leads to brain damage.

11. Thermogenesis Caused by Thyroid Hormones Thyroid hormones are intimately involved in regulating the basal metabolic rate. Liver tissue of animals given excess thyroxine shows an increased rate of O_2 consumption and increased heat output (thermogenesis), but the ATP concentration in the tissue is normal. Different explanations have been offered for the thermogenic effect of thyroxine. One is that excess thryroxine causes uncoupling of oxidative phosphorylation in mitochondria. How could such an effect account for the observations? Another explanation suggests that the thermogenesis is due to an increased rate of ATP utilization by the thyroxine-stimulated tissue. Is this a reasonable explanation? Why?

12. Function of Prohormones What are the possible advantages in the synthesis of hormones as prohormones?

13. Sources of Glucose during Starvation The typical human adult uses about 160 g of glucose per day, 120 g of which is used by the brain. The available reserve of glucose (~20 g of circulating glucose and ~190 g of glycogen) is adequate for about one day. After the reserve has been depleted during starvation, how would the body obtain more glucose?

14. Parabiotic *ob/ob* mice By careful surgery, researchers can connect the circulatory systems of two mice so that the same blood circulates through both animals. In these **parabiotic** mice, products released into the blood by one animal reach the other animal via the shared circulation. Both animals are free to eat independently. If an *ob/ob* mouse (both copies of the *OB* gene are defective) and a normal *OB/OB* mouse (two good copies of the *OB* gene) were made parabiotic, what would happen to the weight of each mouse?



The bacterial RNA polymerase