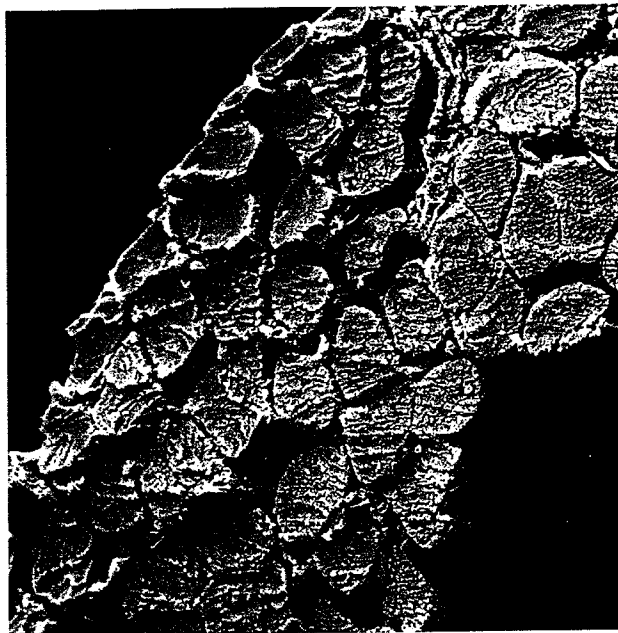


- Interrelationship of Carbohydrate, Lipid, and Protein Metabolism**
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*Human skeletal muscle tissue*

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# CHAPTER

## Integration and Regulation of Metabolism and the Impact of Exercise and Sport

CHAPTERS 4, 6, AND 7 FEATURED carbohydrate, lipid, and protein metabolism at the level of the individual cell, with emphasis on metabolic pathways common to nearly all eukaryotic cells. Those chapters also discussed how the pathways are regulated at the level of certain regulatory enzymes by substrate availability, allosteric mechanisms, and covalent modifications such as phosphorylation.

For their significance to be fully appreciated, metabolic pathways—and the specific metabolic roles of different organs and tissues—must be viewed in the context of the whole organism. Therefore, in this chapter we will examine (1) how the major organs and tissues interact through integration of their metabolic pathways, (2) hormonal regulation of these metabolic processes in maintaining homeostasis, and (3) examples of the body's ability to maintain homeostasis under special circumstances of fasting and intense exercise. The pathways themselves are not reproduced again in this chapter. When appropriate, the reader will be referred to pertinent sections in previous chapters where the pathways are described. A section on the currently attractive field of sports nutrition is included at the end of this chapter. This topic is presented at this point in the text



not only functions in the oxidative catabolism of carbohydrates, fatty acids, and amino acids, but also provides precursors for many biosynthetic pathways, particularly gluconeogenesis (Fig. 4.14). Along with pyruvate, several Krebs cycle intermediates—including  $\alpha$ -ketoglutarate, succinate, fumarate, and oxaloacetate—can be formed from the carbon skeletons of certain amino acids and can function as gluconeogenic precursors.

The fact that animals can be fattened on a predominantly carbohydrate diet is evidence of the apparent ease by which carbohydrate can be converted to fat. However, it is believed that, in the human, lipogenesis from glucose may be much less efficient than previously proposed [1] and that weight gain from carbohydrate is probably due to a sparing of lipolysis rather than direct carbohydrate lipogenesis [2]. Glucose is the precursor for both the glycerol and the fatty acid components of triacylglycerols. The glycerol portion can be formed from dihydroxyacetone phosphate (DHAP), a three-carbon intermediate in glycolysis (see Fig. 4.14). Reduction of DHAP by glycerol 3-phosphate dehydrogenase and NADH produces glycerol 3-phosphate, to which CoA-activated fatty acids attach in the course of triacylglycerol synthesis (see Fig. 6.33). A most significant reaction linking glucose metabolism to fatty acid synthesis is the reaction of the pyruvate dehydrogenase complex, which converts pyruvate to acetyl CoA by dehydrogenation and decarboxylation. Acetyl CoA is the starting material for the synthesis of long-chain fatty acids as well as a variety of other lipids (Fig. 6.30 and Fig. 8.2).

Although carbohydrate can be converted into both the glycerol and the fatty acid components of fat, only the glycerol portion of fat can be converted to carbohydrate. The conversion of fatty acids into carbohydrate is not possible because *the pyruvate dehydrogenase reaction is not reversible*. This prevents the direct conversion of acetyl CoA, the sole catabolic product of even-numbered-carbon fatty acids, into pyruvate for gluconeogenesis. In addition, gluconeogenesis from acetyl CoA as a Krebs cycle intermediate cannot occur, because for every two carbons in the form of acetyl CoA entering the cycle, two carbons are lost by decarboxylation in early reactions of the Krebs cycle (see Fig. 4.15). Therefore, there can be no net conversion of acetyl CoA to pyruvate or to the gluconeogenic intermediates of the cycle. Consequently, acetyl CoA produced from whatever source must be used for energy, lipogenesis, cholesterogenesis, or ketogenesis.

Although fatty acids having an even number of carbons are degraded exclusively to acetyl CoA and therefore are not glucogenic (gluconeogenic) for the reasons mentioned, fatty acids possessing an odd number of carbon atoms are partially glucogenic. This is because

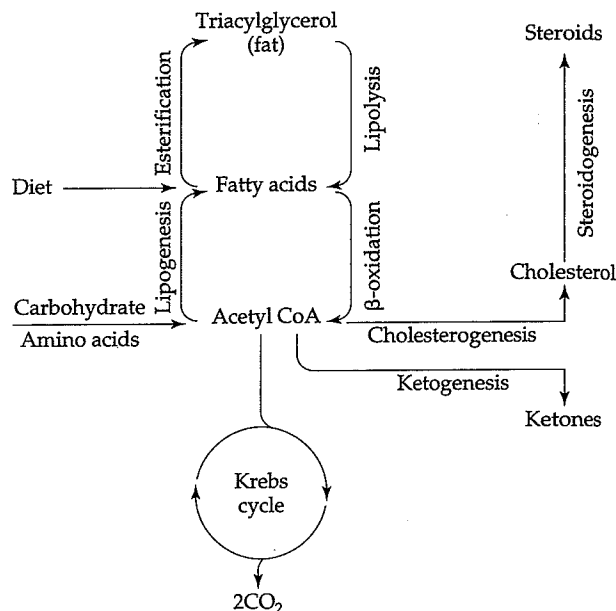


Figure 8.2 Overview of lipid metabolism, emphasizing the central role of acetyl CoA.

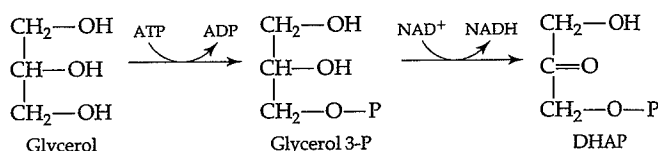


Figure 8.3 Phosphorylation and oxidation of glycerol.

propionyl CoA ( $\text{CH}_3\text{—CH}_2\text{—COSCoA}$ ), ultimately formed by  $\beta$ -oxidation, is carboxylated and rearranged to succinyl CoA, a glucogenic Krebs cycle intermediate (see Fig. 6.26). Fatty acids with an odd number of carbon atoms are not common in the diet.

The glycerol portion of all triacylglycerols is glucogenic, entering the glycolytic pathway at the level of DHAP (see Fig. 4.14). Following its release from triacylglycerol by lipase hydrolysis, glycerol can be phosphorylated to glycerol 3-phosphate by glycerokinase, then oxidized to DHAP by glycerol 3-phosphate dehydrogenase (Fig. 8.3). During the fasting state, when fat catabolism is accelerated, this conversion assumes greater importance in maintaining a normal level of blood glucose.

Metabolism of the amino acids gives rise to a variety of amphibolic intermediates, some of which produce glucose while others produce the ketone bodies via their conversion to acetyl CoA or acetoacetyl CoA (see Fig. 6.27). The catabolism of the individual amino acids is covered in Chapter 7. It is important to remember that amino acids that can be used for production of glucose are termed glucogenic, while those producing ketones

are called ketogenic. Only the amino acids leucine and lysine are purely ketogenic. The dispensable (nonessential) glucogenic amino acids are usually interconverted with carbohydrate, but like the ketogenic amino acids they can be converted (indirectly, however) into fatty acids via acetyl CoA. The fatty acids, however, cannot be converted into the glucogenic amino acids for the same reason that fatty acids cannot form glucose—namely, the irreversibility of the pyruvate dehydrogenase reaction. Although entirely possible, the conversion of the glucogenic amino acids into fat is rather uncommon. Only when protein is supplying a high percentage of calories would glucogenic amino acids be expected to be used in fat synthesis. All the amino acids producing acetyl CoA directly— isoleucine, threonine, phenylalanine, tyrosine,\* lysine, and leucine—are indispensable.

The interconversion of the energy-producing nutrients appears to be skewed toward providing the organism with an energy source that can be easily stored (fat), thereby providing for times when food is not readily available. Energy released by the catabolic processes of the major nutrients must be shared by the energy-requiring synthetic pathways discussed earlier. On reaching the cells, the energy-producing nutrients can be catabolized to produce phosphorylative energy (ATP) and/or reductive energy (NADH, NADPH, FADH<sub>2</sub>). Alternatively, the energy-producing nutrients may be synthesized into more complex organic compounds and/or macromolecules that become cellular components. For synthesis of a cellular component to occur, however, chemical energy must be provided. Therefore, when the cell places priority on the synthesis of a particular component, another energy-producing material must be catabolized. The common energy pool within a cell is finite, and all anabolic and endergonic processes compete for this energy. For example, when the liver is producing more glucose by reversing glycolysis (i.e., gluconeogenesis), it cannot be synthesizing lipids and proteins at the same time. Instead, some of the existing cellular proteins or lipids are hydrolyzed, and the resulting amino acids or fatty acids are oxidized to generate the NADH and ATP needed for gluconeogenesis. Likewise, when hepatic lipogenesis occurs, glucose must be used to produce the NADPH and ATP necessary for the conversion of acetyl CoA to fatty acids.

The final common catabolic pathway for carbohydrate, fat, and protein is the Krebs cycle and oxidative

phosphorylation via the electron transport chain (Figs. 4.15 and 3.16). In addition to releasing energy, these mitochondrial processes are crucial for many other metabolic sequences:

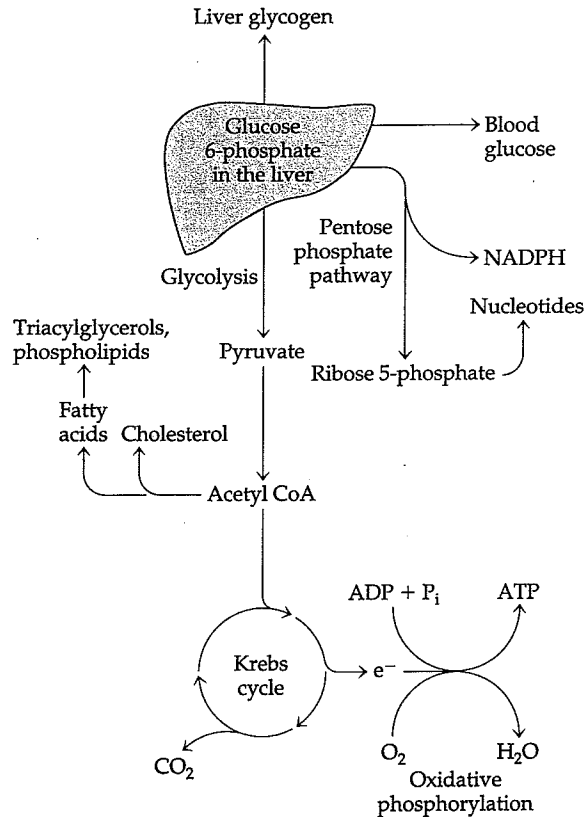
- CO<sub>2</sub> produced by oxidation of acetyl CoA is a source of cellular carbon dioxide for carboxylation reactions that initiate fatty acid synthesis and gluconeogenesis. This CO<sub>2</sub> also supplies the carbon of urea and certain portions of the purine and pyrimidine rings (Figs. 7.16, 7.17, 7.23).
- The Krebs cycle provides common intermediates that provide the cross-linkages between lipid, carbohydrate, and protein metabolism, as illustrated in Figure 8.1. Particularly notable intermediates are  $\alpha$ -ketoglutarate and oxaloacetate. Another interrelationship, not shown in Figure 8.1, is that between heme and an intermediate of the Krebs cycle, succinyl CoA. The initial step in heme biosynthesis is the formation of  $\alpha$ -aminolevulinic acid from "active" succinate and glycine.
- Krebs cycle intermediates—citrate and malate—intermesh with lipogenesis. Citrate can move from the mitochondria into the cytoplasm, where citrate lyase cleaves it into oxaloacetate and acetyl CoA, the initiator of fatty acid synthesis. Malate, in the presence of NADP<sup>+</sup>-linked malic enzyme, may provide a portion of the NADPH<sup>+</sup> required for reductive stages of fatty acid synthesis.

## THE CENTRAL ROLE OF THE LIVER IN METABOLISM

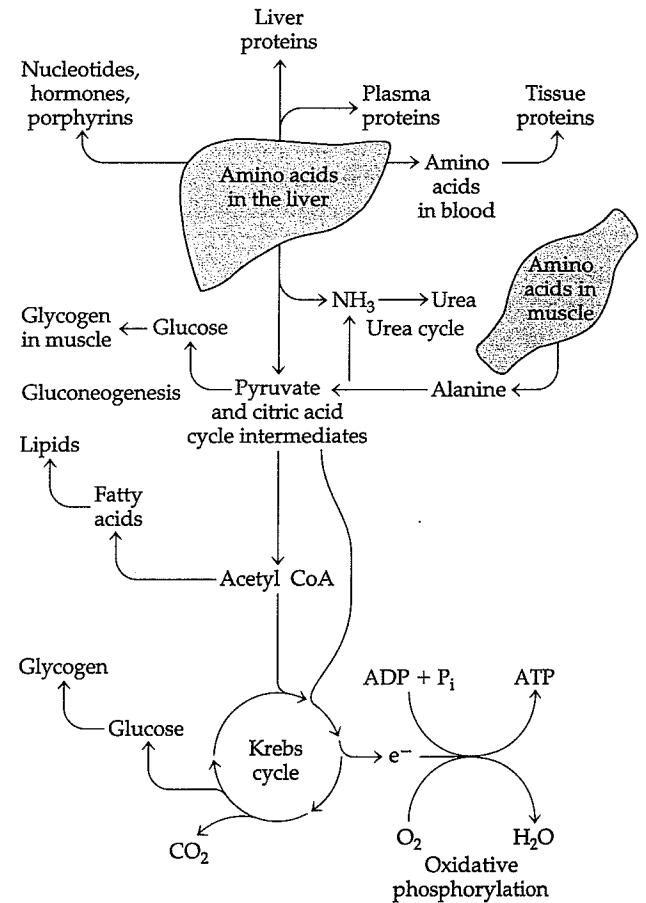
Each tissue and organ of the human body has a specific function that is reflected in its anatomy and its metabolic activity. For example, skeletal muscle uses metabolic energy to perform mechanical work, the brain uses energy to pump ions against concentration gradients in the transfer of electrical impulses, and adipose tissue serves as a depot for stored fat, which on release provides fuel for the rest of the body. Central to all these processes is the liver. It plays the key role of processor and distributor in metabolism, furnishing by way of the bloodstream a proper combination of nutrients to all other organs and tissues. The liver thus warrants special attention in a discussion of tissue-specific metabolism.

Figures 8.4, 8.5, and 8.6 illustrate the fate of glucose 6-phosphate, amino acids, and fatty acids, respectively, in the liver. In these figures, anabolic pathways are shown pointing upward; catabolic pathways, pointing down; and distribution to other tissues, running horizontally.

\*Tyrosine is formed by hydroxylation of phenylalanine; therefore, its carbon skeleton cannot be synthesized in the body but must be obtained from food.



**Figure 8.4** Metabolic pathways for glucose 6-phosphate in the liver. Here and in Figures 8.5 and 8.6, anabolic pathways are shown pointing upward; catabolic pathways, downward; and distribution to other tissues, horizontally.



**Figure 8.5** Pathways of amino acid metabolism in the liver.

The pathways indicated are described in detail in Chapters 4, 6, and 7, which deal with carbohydrate, lipid, and protein metabolism, respectively.

Glucose entering the hepatocytes is phosphorylated by glucokinase to glucose 6-phosphate. Other dietary monosaccharides (fructose, galactose, and mannose) are also phosphorylated and rearranged to glucose 6-phosphate. Figure 8.4 shows the possible metabolic routes available to glucose 6-phosphate. Liver glycogenesis likely occurs primarily from newly synthesized glucose derived from gluconeogenic precursors delivered to the hepatocytes from peripheral tissues rather than through preformed glucose directly [3] (see also Fig. 4.11). This finding is referred to again in the following section.

Figure 8.5 reviews the particularly active role of the liver in amino acid metabolism. The liver is the site of synthesis of many different proteins, both structural and plasma-borne, from amino acids. Amino acids also can be converted in the liver into nonprotein products such as nucleotides, hormones, and porphyrins. Catabolism of amino acids can take place in the liver, where most are transaminated and degraded to acetyl

CoA and other Krebs cycle intermediates. These in turn can be oxidized for energy or converted to glucose or fat. Glucose formed from gluconeogenesis can be transported to muscle for use by that tissue. Newly synthesized fatty acids can be mobilized to adipose tissue for storage or used as fuel by muscle. Hepatocytes are the exclusive site for the formation of urea, the major excretory form of amino acid nitrogen.

The fate of fatty acids entering the liver is outlined in Figure 8.6. Fatty acids can be assembled into liver triacylglycerols or released into the circulation as plasma lipoproteins. In humans, most fatty acid synthesis takes place in the liver rather than in adipocytes. Adipocytes store triacylglycerols arriving from the liver, primarily in the form of plasma VLDLs, and from the lipoprotein lipase action on chylomicrons. Under most circumstances, fatty acids are the major fuel supplying energy to the liver by oxidation. Acetyl CoA not used for energy can be used for the formation of the ketone bodies, which are very important fuels for certain peripheral tissues such as the brain and heart muscle, particularly during periods of prolonged fasting.

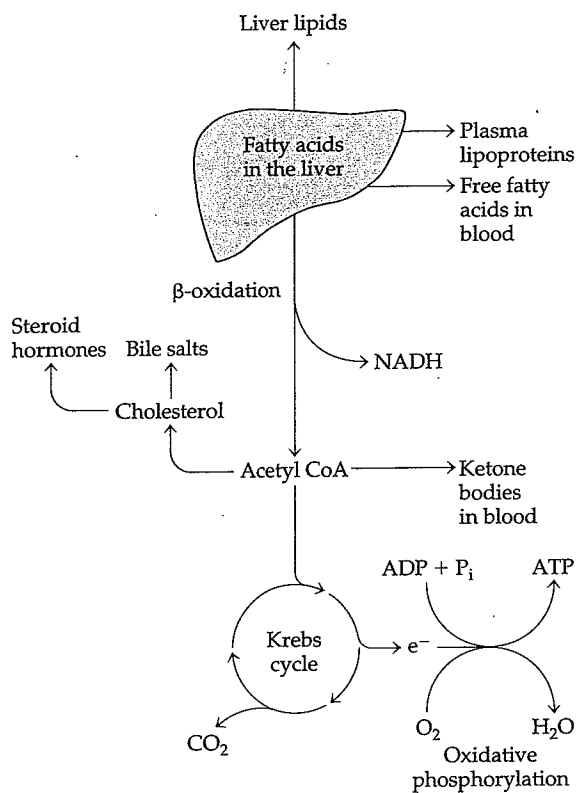


Figure 8.6 Pathways of fatty acid metabolism in the liver.

## TISSUE-SPECIFIC METABOLISM DURING THE FED-FAST CYCLE

### Carbohydrate and Lipid Metabolism

The best way to appreciate the interrelationship of metabolic pathways and the involvement of different organs and tissues in metabolism is to gain an understanding of the fed-fast cycle. The human typically eats specific meals followed by a period of not eating. Food consumption is often 100 times greater than basic caloric needs during the short period of time the meal is consumed, allowing humans to survive from meal to meal without nibbling continuously. Because glucose is a major fuel for tissues, it is very important that glucose homeostasis be maintained whether food has just been consumed or a state of fasting exists. If the period since the last meal is short (less than 18 hours), the mechanisms used to maintain glucose homeostasis are different from those used if the fasting state is prolonged. During prolonged fasts, other fuels gain importance. The extent to which different organs are involved in carbohydrate and fat metabolism varies within the fed-fast cycles that underlie the eating habits of the human being. When energy consumption exceeds expenditures, the excess calories are stored as glycogen and fat, which can be used

as needed. A fed-fast cycle can be divided into four states, or phases:

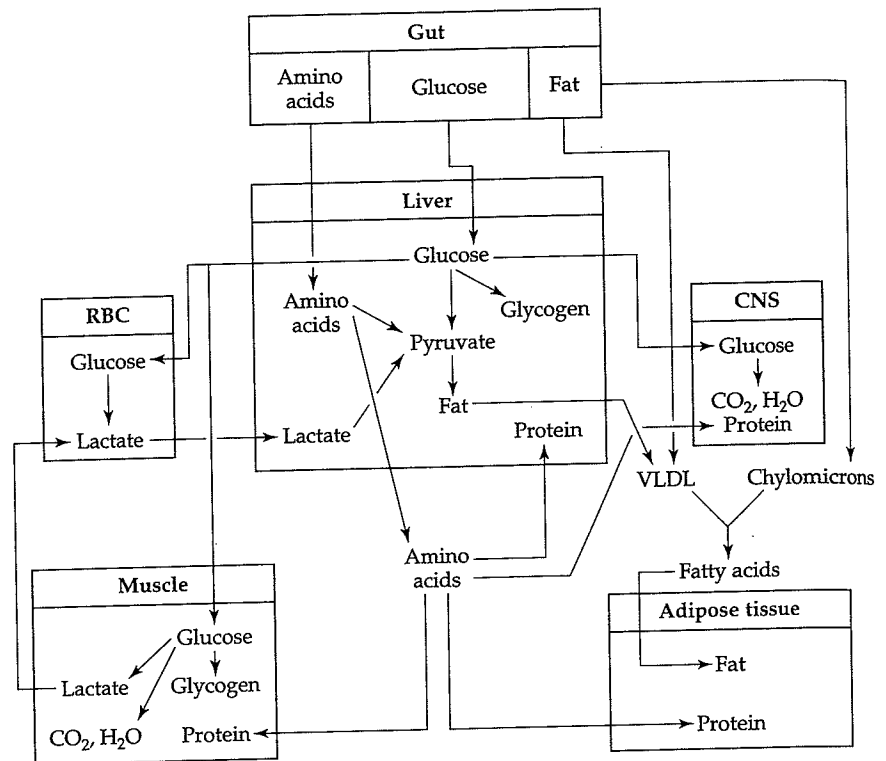
1. The fed state, lasting about 3 hours after the ingestion of a meal
2. The postabsorptive or early fasting state, occurring during a time span of from 3 hours to about 12 to 18 hours following the meal
3. The fasting state, lasting from about 18 hours up to about 2 days without additional intake of food
4. The starvation state or long-term fast, a fully adapted state of food deprivation lasting as long as several weeks

Clearly, in a normal eating routine only the fed and early fasting states apply. The time frames of the phases cited are only approximate and are strongly influenced by factors such as activity level, the caloric value and nutrient composition of the meal, and the subject's metabolic rate.

### The Fed State

Figure 8.7 illustrates the disposition of glucose, fat, and amino acids among the various tissues during the fed state. The red blood cells (RBCs) do not have mitochondria and can burn glucose only anaerobically. The central nervous system (CNS) has no metabolic mechanisms by which glucose can be converted to energy stores, nor can it make glycogen or store triacylglycerols. Glucose available to these tissues is oxidized immediately to produce energy. In the liver, in contrast, some glucose can be converted directly to glycogen. Contrary to the conventional view of liver glycogenesis, however, research indicates that most liver glycogen is synthesized indirectly from gluconeogenic precursors (pyruvate, alanine, and lactate) returning to the liver from the periphery rather than directly from glucose entering the liver via the portal vein [3]. A likely source of lactate for the liver is the red blood cells, as indicated in Figure 8.7. The reason why glucose is not used well as a direct precursor of glycogen has been attributed to the low phosphorylating activity of the liver at physiological concentrations of glucose [4].

The liver is the first tissue to have the opportunity to use dietary glucose. In the liver, glucose can be converted to glycogen. When available glucose or its gluconeogenic precursors exceed the glycogen storage capacity of the liver, the excess glucose can be metabolized in a variety of ways, as shown in Figure 8.4 and in somewhat more detail in Figure 8.7. The conversion of glucose to fatty acids and glycogen is important because both represent the storage of glucose carbon. The conversion of glucose to fatty acids appears to occur only if energy intake exceeds energy expenditure. The potential conversion of excess glucose to fatty acids is particularly crucial because these fatty acids, along with



**Figure 8.7** Disposition of dietary glucose, amino acids, and fat in the fed state.

those removed from the chylomicrons and VLDL by lipoprotein lipase, can be stored in the adipose tissue, thereby providing a ready source of fuel for most body tissues during the postabsorptive and fasting states.

Some exogenous glucose—that coming from the intestine—bypasses the liver and circulates to other tissues. The brain and other tissues of the central nervous system are almost solely dependent on glucose as an energy source during the fed and postabsorptive states. Other major users of glucose include

- the RBCs, which, lacking mitochondria, convert it via the glycolytic pathway to lactate for the small amount of energy the cell requires and also use it as a source of NADPH via the hexosemonophosphate shunt;
- adipose tissue, which can use glucose to some extent as a precursor for both the glycerol and the fatty acid components of triacylglycerols (although, in the human, most triacylglycerols are synthesized by the liver and transported to the adipose tissue); and
- muscle, which uses glucose for the synthesis of glycogen and for the production of energy.

With the exception of the RBCs, all the tissues included in Figure 8.7 actively catabolize glucose for energy via the Krebs cycle.

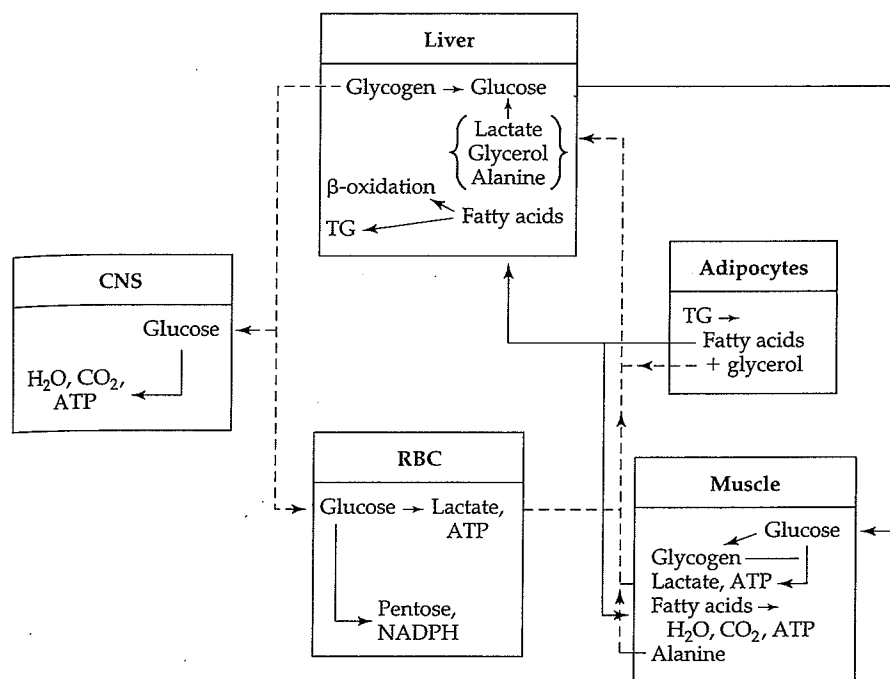
In considering fat delivery to the tissues, it is necessary to differentiate between exogenous and endogenous fat.

Dietary fat, except for short-chain fatty acids, enters the bloodstream as chylomicrons, which are promptly acted on by lipoprotein lipase from the vascular endothelium, releasing free fatty acids and glycerol (Chapter 6). Chylomicron remnants remaining from this hydrolysis are taken up by the liver, and their lipid contents are transferred to the very low density lipoprotein fraction. Endogenous fatty acids of the serum are taken up by the adipocytes, reesterified with glycerol to form triacylglycerols, and stored as such as large fat droplets within the cells.

### The Postabsorptive or Early Fasting State

With the onset of the postabsorptive state, tissues can no longer derive their energy directly from ingested glucose and other macronutrients but instead must begin to depend on other sources of fuel (Fig. 8.8). During the short period of time marking this phase (a few hours after eating), hepatic glycogenolysis is the major provider of glucose to the blood, which serves to deliver it to other tissues for use as fuel. When glycogenolysis is occurring, the synthesis of glycogen and triacylglycerols in the liver is diminished, and the *de novo* synthesis of glucose (gluconeogenesis) begins to help maintain blood glucose levels.

Lactate, formed in and released by RBCs and muscle tissue, becomes an important carbon source for hepatic gluconeogenesis. The glucose-alanine cycle, in which



**Figure 8.8** The primary postabsorption flow of substrates among the liver, CNS, adipose tissue, muscle, and red blood cells. *Source:* Modified from Zakim D, Boyer T. eds. *Hepatology: A Textbook of Liver Disease*, 4th ed. Philadelphia: WB Saunders, 2003.

carbon in the form of alanine returns to the liver from muscle cells, also becomes important. The alanine is then converted to pyruvate as the first step in the gluconeogenic conversion of alanine in the liver. The alanine cannot be converted to glucose in the muscle. In the postabsorptive state, glucose provided to the muscle by the liver comes primarily from the recycling of lactate and alanine and to a lesser extent from hepatic glycogenolysis. Muscle glycogenolysis provides glucose as fuel only for muscle cells in which the glycogen is stored, because muscle lacks the enzyme glucose 6-phosphatase. Once phosphorylated in the muscle, glucose is trapped there and cannot leave except as three-carbon units of lactate or alanine.

The brain and other tissues of the CNS are extravagant consumers of glucose, oxidizing it for energy and releasing no gluconeogenic precursors in return. The rate of glucose use is greater than the rate of glucose production by gluconeogenesis, and the stores of liver glycogen begin to diminish rapidly. In the course of an overnight fast, nearly all reserves of liver glycogen and most muscle glycogen have been depleted. Figure 8.8 shows the shifts of metabolic pathways that occur in the tissues during the postabsorptive state.

### The Fasting State

The postabsorptive state evolves into the early fasting state after 18 to 48 hours of no food intake. Particularly notable in the liver is the *de novo* glucose synthesis (gluconeogenesis) occurring in the wake of glycogen depletion (Fig. 8.9). Amino acids from muscle protein

breakdown provide the chief substrate for gluconeogenesis, although the glycerol from lipolysis and the lactate from anaerobic metabolism of glucose also are used to some extent.

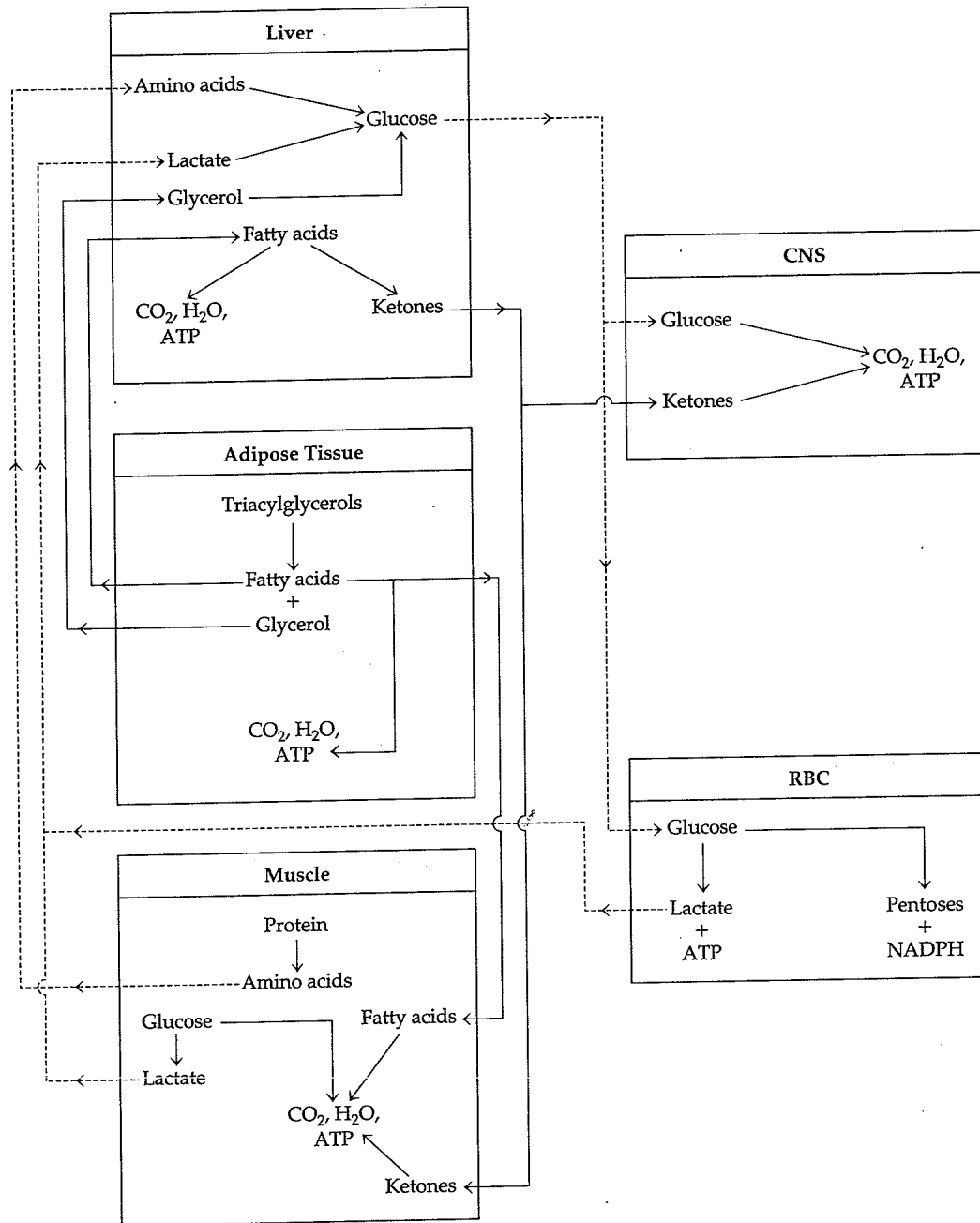
The shift to gluconeogenesis during prolonged fasting is signaled by the secretion of the hormone glucagon and the glucocorticosteroid hormones in response to low levels of blood glucose. Proteins are hydrolyzed in muscle cells at an accelerated rate to provide the gluconeogenic amino acids. Of all the amino acids, only leucine and lysine cannot contribute at all to gluconeogenesis because, as noted previously, these amino acids are totally ketogenic. However, ketogenic amino acids released by muscle protein hydrolysis serve a purpose as well. Because they are converted into ketones—that is, acetyl CoA, acetoacetyl CoA, or acetoacetate—they allow the brain, heart, and skeletal muscle to adapt to the use of these substrates should the nutritive state continue to deteriorate into a state of long-term fast or starvation.

The early fasting state is accompanied by large daily losses of urinary nitrogen, in keeping with the high rate of breakdown of muscle protein and the synthesis of glucose through hepatic gluconeogenesis.

### The Starvation State

If the fasting state persists and progresses into a starvation state (often referred to as a long-term fast), a metabolic fuel shift occurs again, this time in an effort to spare body protein. This new priority is justified by the vital physiological importance of body proteins. Proteins that





**Figure 8.9** Flow of substrates among the liver, CNS, adipose tissue, muscle, and red blood cells during fasting and starvation states. Broken lines indicate major substrate flow during fasting lasting about 2 days. Solid lines reflect predominant substrate flow during the starvation state. Notice the shift during starvation to fatty acid and glycerol export from adipose tissue and the increased use of fatty acids and ketones as fuel by CNS and muscle.

must be conserved for life to continue include antibodies, needed to fight infection; enzymes, which catalyze life-sustaining reactions; and hemoglobin, necessary for the transport of oxygen to tissues. The protein-sparing shift at this point is from gluconeogenesis to lipolysis, as the fat stores become the major supplier of energy. Fat

stores, deposited when more calories were consumed than expended, are large in most individuals. The blood level of fatty acids increases sharply, and fatty acids become the primary fuel for heart, liver, and skeletal muscle tissues that oxidize them for energy. The brain cannot use fatty acids for energy because fatty acids

cannot cross the blood-brain barrier. However, the shift to fat breakdown also releases a large amount of glycerol, which replaces amino acids as the major gluconeogenic precursor, assuring a continued supply of glucose as fuel for the brain. The brain and skeletal muscle also adapt to use ketone bodies for energy.

Eventually, the use of Krebs cycle intermediates for gluconeogenesis depletes the supply of oxaloacetate. Low levels of oxaloacetate, coupled with the rapid production of acetyl CoA from fatty acid catabolism, cause acetyl CoA to accumulate, favoring the formation of acetoacetyl CoA and the ketone bodies. Ketone body concentration in the blood then rises (ketosis) as these fuels are exported from the liver, which cannot use them. They are delivered through the bloodstream to the skeletal muscle, heart, and brain, which oxidize them instead of glucose. As long as ketone bodies are maintained at a high level by hepatic fatty acid oxidation, the need for glucose and gluconeogenesis is reduced, thereby sparing valuable protein. Figure 8.9 illustrates the changes in energy metabolism that occur in various tissues during the fasting and starvation states.

Survival time in starvation depends mostly on the quantity of fat stored before starvation. Stored triacylglycerols in the adipose tissue of an individual of normal weight and adiposity can provide enough fuel to sustain basal metabolism for about 3 months. A very obese adult probably has enough fat calories stored to endure a fast of more than a year, but physiological damage and even death could result from the accompanying extreme ketosis. When fat reserves are gone, the degradation of essential protein begins, leading to loss of liver and muscle function and, ultimately, death [5].

### Amino Acid Metabolism

Organ interactions in amino acid metabolism, illustrated in Figure 8.10, are largely coordinated by the liver. The pathways shown undergo regulatory adjustments after consumption of a meal containing protein.

In the fed state, absorbed amino acids pass into the liver, where the fate of most of them is determined in relation to needs of the body. Amounts in excess of need are degraded. Only the branched-chain amino acids (BCAAs) are not regulated by the liver according to the body's needs. Instead, the BCAAs pass to the periphery, primarily to the muscles and adipose tissue, where they may be metabolized. Of particular interest is the fate of the BCAAs that reach the muscle. These amino acids are usually greatly in excess of the need for muscle protein synthesis. The excess is believed to be used for synthesis of the dispensable amino acids needed for the increase in protein synthesis that occurs after a protein meal.

The liver is the site of urea synthesis, the primary mechanism for disposing of the excess nitrogen derived

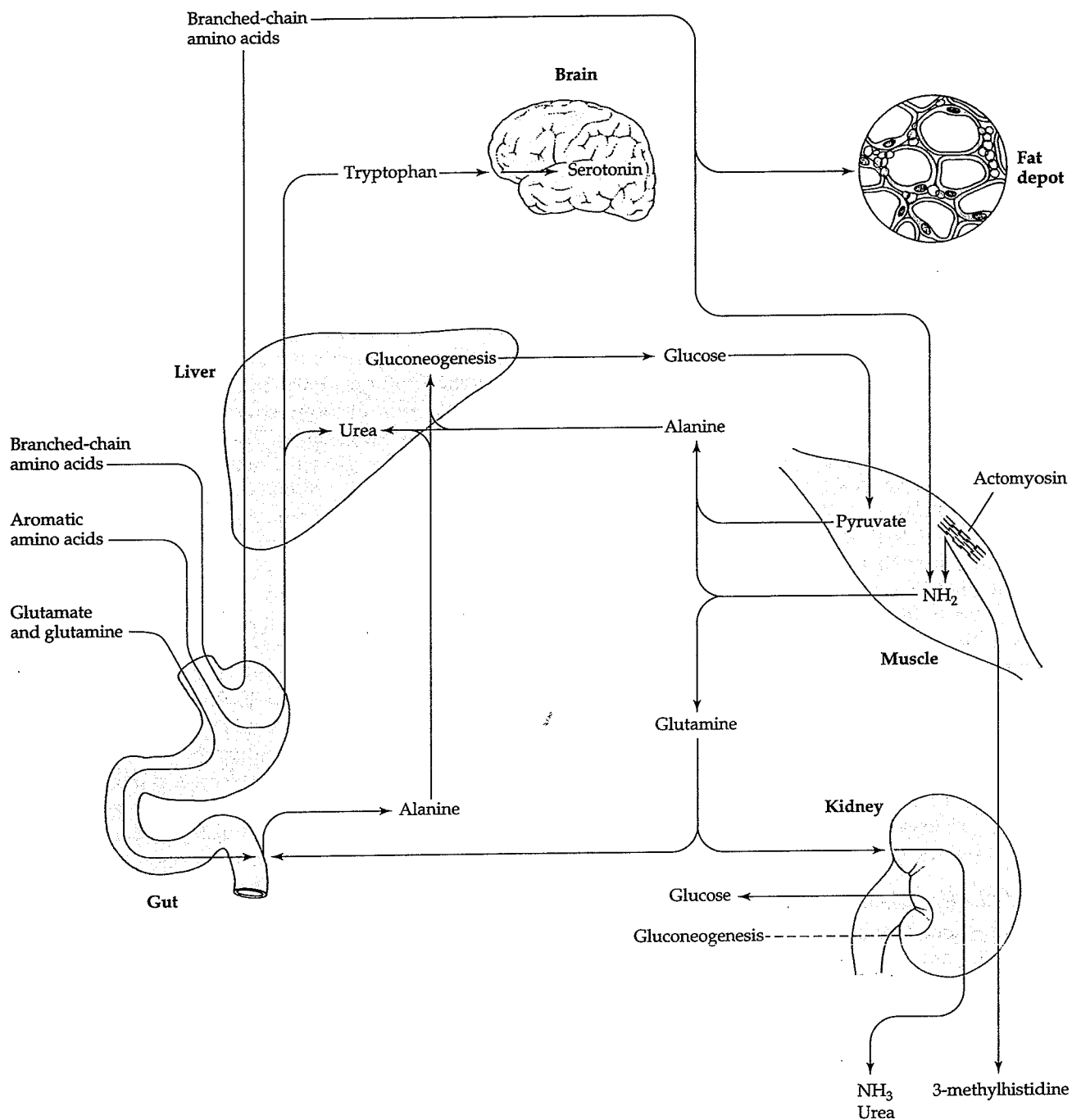
from amino acids used for energy or gluconeogenesis. (Chap. 7 describes how urea is formed.) The liver is active in removing the nitrogen from amino acids and uses the  $\alpha$ -keto acids (amino acids from which the amine group has been removed) as the chief substrate. During fasting, gluconeogenesis becomes a very important metabolic pathway in the regulation of plasma glucose levels, and even more nitrogen is available for excretion. Kidney gluconeogenesis is accompanied by the formation and excretion of ammonia.

The importance of the liver to the functioning of muscle during the fasting state or during very vigorous exercise is exemplified in the alanine-glucose cycle (Fig. 7.34). During periods of fasting or strenuous exercise, the muscle breaks down protein to amino acids. The nitrogen from the amino acids is transaminated to  $\alpha$ -ketoglutarate (formed in the Krebs cycle) to make glutamic acid. The glutamic acid then transaminates its  $\alpha$  amino group to pyruvate (formed from glycolysis) to make alanine. The alanine enters the bloodstream and is transported to the liver, where it again undergoes transamination. Alanine is converted to pyruvate, and  $\alpha$ -ketoglutarate is converted to glutamic acid. This cycle serves several functions. It removes the nitrogen from muscle during a period of high proteolysis and transports it to the liver in the form of alanine. The carbon structure of pyruvate also is transported to the liver, where it can be made into glucose through gluconeogenesis. The synthesized glucose can be transported back to the muscle and used for energy by that tissue. The glucose-alanine cycle also acts as a carrier of amino-nitrogen from intestinal mucosal cells to the liver during periods of amino acid absorption.

Glutamine also plays a central role in the transport and excretion of amino acid nitrogen. Many tissues, including the brain, combine ammonia, released primarily by the glutamate dehydrogenase reaction, with glutamate to form glutamine. The reaction is catalyzed by glutamine synthetase. In the form of glutamine, ammonia can then be carried to the liver or kidneys for excretion as urea or ammonium ion, respectively. In those tissues, glutamine is acted on by the enzyme glutaminase, releasing the ammonia for excretion and re-forming glutamate. Figure 8.10 gives an overview of organ cooperation in these and other aspects of amino acid metabolism. See Chapter 7 for a more detailed discussion of amino acid metabolism in general.

### SYSTEM INTEGRATION AND HOMEOSTASIS

Integration of the metabolic processes, as outlined in the preceding sections, allows the "constancy of the internal milieu" of humans and other multicellular organisms that was described by the French physiologist Claude



**Figure 8.10** Interchanges of selected amino acids and their metabolites among body organs and tissue. *Source:* Modified from Munro HN. Metabolic integration of organs in health and diseases. *J Parent Enter Nutr* 1982;6:271-79. © American Society of Parenteral and Enteral Nutrition. Used with permission.

Bernard about a century ago. This integration of metabolism at the cellular and the organ and tissue levels, which is essential for the survival of the entire organism, receives its direction via body systems. The integration of body systems makes possible communication among all parts of the body.

Three major systems direct activities of the cells, tissues, and organs to ensure their harmony with the whole organism: the nervous, endocrine, and vascular systems.

The **nervous system** is considered the primary communication system because it not only has receiving mechanisms to assess the body's status in relation to its

environment but also has transmitting processes to relay appropriate commands to various tissues and organs. The nervous system can inform the body of conditions such as hunger, thirst, pain, and lack of oxygen. This information allows organs to adjust to external changes and may initiate appropriate behavior by the whole organism. Tepperman and Tepperman [6] compare the nervous system to an elaborate system of telegraphy that has a "wire" connection from the source of message initiation to the place where message reception has its needed effect.

The **endocrine system** [6] is compared to a wireless system that transmits messages via highly specialized substances called hormones. The endocrine system depends on the vascular system to carry messages to target tissues.

The **vascular system** is comparable to a plumbing system with flexible pipes. It is the primary transport mechanism for the body, not only delivering specialized chemical substances but also carrying oxygen, organic nutrients, and minerals from the external environment to cells throughout the body. It also transports the waste products of metabolism from the cells, carrying them to the lungs and/or kidneys for elimination.

The concentration of solutes in the blood must be regulated within a narrow range. Among the most prominent sentinel cells that monitor and regulate solute concentration are those that synthesize and secrete hormones. Although hormone synthesis and secretion occur primarily in the endocrine system, considerable overlap exists between the endocrine system and the CNS. With the recent discovery of a variety of neuropeptides and recognition of the hormonal action of many of these peptides, it has become apparent that the CNS and the endocrine system are functionally interdependent [6,7].

Tissues and cells that respond to hormones are called the target tissues and cells of the hormones. These hormone-responsive cells have been preprogrammed by the process of differentiation to respond to the presence of hormones by acting in a predictable way. Not only do hormone-responsive cells respond to hormones via specific receptors, but their metabolic pathways also can be affected by the concentration of available substrates. Hormone-responsive cells live in a complex and continually changing environment of fuels and ions. Their ultimate response to these changes is the net result of both hormonal and nonhormonal information brought to them by the extracellular fluids in which they are bathed [6]. The response of the endocrine system to this information is discussed next.

### Endocrine Function in Fed State

Endocrine organs are distributed throughout the body, and most are involved primarily with nutrient

ingestion—that is, the gastrointestinal (GI) tract. Interspersed among the absorptive and exocrine secretory cells of the upper GI tract are the highly specialized endocrine cells. These cells present a sensor face to the lumen and secrete granule-stored hormones into the bloodstream. Each of these cells is stimulated to secrete hormones by a different combination of chemical messages. Chemical messages include, for example, glucose, amino acids, fatty acids, and alkaline or acid pH. Hormones secreted by these stimulated GI cells (GIP, CCK, gastrin, secretin) (Table 2.1) then enter the bloodstream and sensitize appropriate cells of the endocrine pancreas for response to the approaching nutrients. The primary action of the GI hormones, secreted in response to a mixed diet, is to amplify the response of the pancreatic islet  $\beta$ -cells to glucose [6].

Insulin, secreted by the  $\beta$ -cells, is the hormone primarily responsible for the direction of energy metabolism during the fed state (Fig. 8.7). Its effects can be categorized, based on the time of action, as (1) very fast, occurring in a matter of seconds; (2) fast, occurring in minutes; (3) slower, occurring in minutes to several hours; (4) slowest, occurring only after several hours or even days.

An example of a very fast action of insulin is membrane changes stimulated by the hormone. These changes occur in specific cells where glucose entry depends on membrane transport (see the section "Glucose Transporters" in Chap. 4). The fast action of insulin involves the activation or inhibition of many enzymes, with anabolic actions accentuated. For example, insulin stimulates glycogenesis, lipogenesis, and protein synthesis while it inhibits opposing catabolic actions. Several metabolic effects of insulin and the corresponding target enzymes involved are listed in Table 8.1. Insulin favors glycogenesis through the activation of a phosphatase that dephosphorylates phosphorylase and glycogen synthase. This dephosphorylation activates glycogen synthetase while inhibiting the phosphorylase

**Table 8.1** Metabolic Effects of Insulin and Its Action on Specific Enzymes

Metabolic Effect	Target Enzyme
↑ Glucose uptake (muscle)	↑ Glucose transporter
↑ Glucose uptake (liver)	↑ Glucokinase
↑ Glycogen synthesis (liver, muscle)	↑ Glycogen synthase
↓ Glycogen breakdown (liver, muscle)	↓ Glycogen phosphorylase
↑ Glycolysis, acetyl CoA production (liver, muscle)	↑ Phosphofructokinase-1 ↑ Pyruvate dehydrogenase complex
↑ Fatty acid synthesis (liver)	↑ Acetyl CoA carboxylase
↑ Triacylglycerol synthesis (adipose tissue)	↑ Lipoprotein lipase

that initiates glycogenolysis. The fast effect of insulin on protein synthesis is not as clear-cut as its influence on lipogenesis and glycogenesis. Nevertheless, protein synthesis is promoted and appears to be related to stimulation of the translation process [6].

One slower action of insulin involves a further regulation of enzyme activity. This regulation is accomplished through the selective induction or repression of enzyme synthesis. The induced enzymes are the key rate-limiting enzymes for anabolic reaction sequences, while the repressed enzymes are crucial to the control of opposing catabolic reactions. An example of selective induction is the effect of insulin on glucokinase activity. Insulin increases the synthesis of glucokinase by promoting transcription of the glucokinase gene. Another, slower action of insulin is its stimulation of cellular amino acid influx. The slowest effect of insulin is its promotion of growth through mitogenesis and cell replication. The passage of a cell through its various phases before it can replicate is a relatively slow process that requires 18 to 24 hours for completion.

### Endocrine Function in Postabsorptive or Fasting State

Metabolic adjustments that occur in response to food deprivation operate on two time scales: acutely, measured in minutes (such as adjustments operating in a postabsorptive state), and chronically, measured in hours and days (adjustments occurring during fasting or starvation). In contrast to the fed state, in which insulin is the hormone primarily responsible for the direction of energy metabolism, the body deprived of food requires a variety of hormones to regulate its fuel supply.

Figure 8.8 depicts the postabsorptive state in which hepatic glycogenolysis is providing some glucose to the body while increased use of fatty acids for energy is decreasing the glucose requirement of cells. Also, gluconeogenesis is being initiated, with lactate, glycerol, and alanine serving as substrates.

Hepatic glycogenolysis is initiated through the action of glucagon, which is secreted by the  $\alpha$ -cells of the endocrine pancreas, and of epinephrine (adrenaline) and norepinephrine, which are synthesized primarily in the adrenal medulla and the sympathetic nerve endings, respectively. Epinephrine is considerably more potent in stimulating glycogenolysis than is norepinephrine, which functions mainly as a neurotransmitter. Epinephrine and norepinephrine are called the catecholamine hormones because they are derivatives of the aromatic alcohol catechol. Although they influence hepatic glycogenolysis somewhat, the catecholamines exert their effect primarily on the muscles. The action of

glucagon and the catecholamines is mediated through cAMP and protein kinase phosphorylation. (This mechanism is described in the section on glycogenolysis in Chap. 4; see also Fig. 4.13.) Through the action of glucagon on the liver, phosphorylase and glycogen synthetase are phosphorylated, in direct opposition to the action of insulin. Consequently, phosphorylase is activated and glycogen synthetase is inhibited. As a result, glycogen is broken down, giving rise to glucose 6-phosphate, which then can be hydrolyzed by the specific liver phosphatase (glucose 6-phosphatase) to produce free glucose. The free glucose can then enter the bloodstream to maintain blood glucose levels.

Muscle glycogenolysis, in contrast, stimulated by the catecholamines, provides glucose only for use by the particular muscle in which the glycogen has been stored. Phosphorylated glucose cannot cross the cell membrane. Muscle tissue lacks glucose 6-phosphatase and cannot release free glucose into the circulation. The catecholamines, however, raise blood glucose levels indirectly by stimulating the secretion of glucagon and inhibiting the uptake of blood glucose by the muscles.

Glycogenolysis can occur within minutes and thus meets an acute need for raising the blood glucose level. However, because so little glycogen is stored in the liver (~60–100 g), blood glucose cannot be maintained over a prolonged period. The content of total muscle glycogen is ~350 g. Twelve to 18 hours following a meal, liver glycogen levels are very low. As mentioned previously, gluconeogenesis in the liver is a major supplier of glucose during fasting. Lactate, glycerol, alanine, and other amino acids are the primary precursors. Gluconeogenesis is fostered by the same hormones that initiate glycogenolysis (glucagon and epinephrine), but the amino acids needed as substrates are made available through the action of the glucocorticoids secreted by the adrenal cortex. Glucocorticoid hormones stimulate gluconeogenesis. Alanine, generated in the muscle from other amino acids and from pyruvate by transamination, not only serves as the principal gluconeogenic substrate but also acts as a stimulant of gluconeogenesis via its effect on the secretion of glucagon. In fact, alanine is the prime stimulator of glucagon secretion by  $\beta$ -cells that have been sensitized to the action of alanine by the glucocorticoids.

Low levels of circulating insulin not only decrease the use of glucose but also promote lipolysis and a rise in free fatty acids. Contributing to this effect is the increase in glucagon during the fasting period. Glucagon raises the level of cAMP in adipose cells, and the cAMP then activates a lipase that hydrolyzes stored triacylglycerols. The muscles, inhibited from taking up glucose by the catecholamines, begin to use fatty acids as the major source of energy. This increased use of fatty acids by the

Table 8.2 Fuel Metabolism in Starvation

Fuel Exchanges and Consumption	Amount Formed or Consumed in 24 Hours (g)	
	Day 3	Day 40
Fuel use by the brain		
Glucose	100	40
Ketones	50	100
Fuel mobilization		
Adipose tissue lipolysis	180	180
Muscle protein degradation	75	20
Fuel output of the liver		
Glucose	150	80
Ketones	150	150

Source: Adapted from Stryer L. *Biochemistry*, 3rd ed. New York: Freeman 1988 p. 640.

muscles represents an important adaptation to fasting. Growth hormone and the glucocorticoids foster this adaptation because they, like the catecholamines, inhibit in some manner the use of glucose by the muscles.

As starvation is prolonged, less and less glucose is used, thereby reducing the amount of protein that must be catabolized to provide substrate for gluconeogenesis. As glucose use decreases, hepatic ketogenesis increases and the brain adapts to the use of ketones (primarily  $\beta$ -hydroxybutyrate) as a partial source of energy. After 3 days of starvation, about one-third of the energy needs of the brain are met by ketones. With prolonged starvation, ketones become the major fuel source for the brain. Under conditions of continued carbohydrate shortage, ketones are oxidized by the muscles in preference not only to glucose but also to fatty acids. During starvation, the use of ketones by the muscles as the preferred source of energy spares protein, thereby prolonging life. Although Figure 8.9 depicts fuel metabolism during starvation, it does not show some of the adjustments in energy substrates that occur when starvation is prolonged. These adjustments are shown in Table 8.2. As mentioned previously, the duration of starvation compatible with life depends to a large degree on depot fat status.

## SPORTS NUTRITION

Humans have courted the challenge of athletic performance and competition since the days of the early Greeks. The science of nutrition emerged much later, spurred by the expanding knowledge of metabolism and the biochemistry on which it is based. Because the energy for physical performance must be derived from nutrient intake, it was only a matter of time before these areas of interest would be linked. The heavy emphasis on the enhancement of health and physical performance in today's society has led to the emergence of sports nutrition as an important science. Nutrition, as a means of

positive impact on physical performance, has become a topic of great interest to all those involved in human performance, the scientist as well as the athlete and athletic trainer.

The human body converts the potential energy of nutrients to usable energy, part of which drives the contraction of muscle, a process fundamental to athletic prowess. Fluctuations in the body's demand for energy—for example, changes in exertion level among resting, mild exercise, and strenuous exercise—are accompanied by shifts in the rate of catabolism of the different stored forms of nutrients. It follows that an understanding of sports nutrition requires an understanding of the integration of the metabolic pathways that furnish the needed energy. In this respect, therefore, the energy demands of sport resemble the fed-fast cycle described earlier in this chapter, so a discussion of sports nutrition at this point in the text seems appropriate.

## Biochemical Assessment of Physical Exertion

To fully understand sports nutrition, we need to examine different types of skeletal muscle. A more detailed discussion of this topic can be found in an exercise physiology text (such as [8]). Muscle generally is classified as one of three distinct types, each emphasizing a different metabolic pathway: Type I, Type IIa, and Type IIb. Type I muscle, sometimes called red muscle, is oxidative and red in color. It has a large number of mitochondria and therefore is capable of oxidizing glucose to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  and carrying out  $\beta$ -oxidation of fatty acids. This muscle typically is used for aerobic endurance events. Type IIa muscle and Type IIb muscle have been called white muscle. Type IIb has fewer mitochondria, has a very active glycolytic pathway, and is white in appearance. This type of muscle is used primarily for short-duration anaerobic events and power events. Type IIa muscle can be considered a hybrid of Type I and Type IIb muscle, with some characteristics of each. Endurance training can make Type IIa muscle act more like Type I muscle, while strength training or sprint training can make it look more like Type IIb. Much more could be said about the muscle types and their response to nervous system stimulation and training, but this brief description provides sufficient information to foster an understanding of the resemblance of sports nutrition to the fed-fast cycle.

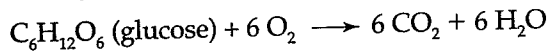
To understand how the muscle types relate to physical exercise at the cellular level, we need to examine two common measurements used by the exercise physiologist [8]: the **respiratory quotient (RQ)** and the maximal oxygen consumption ( **$\text{VO}_2$  max**). Typical RQs for carbohydrate, fat, and protein are 1.0, 0.70, and 0.82, respectively (values are explained below). A newer generation of procedures (e.g., the **isotope infusion method**) has

been developed to measure the relative contribution of substrates to energy supply during exercise. These measurements will be described briefly here. Further details of how the duration and intensity of physical conditioning influence which muscle cell type is used and which metabolic pathways are active are discussed in the perspective "Nutrient Usage during Strenuous Exercise" at the end of this chapter.

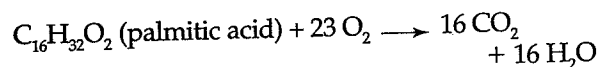
The respiratory quotient (RQ) is the ratio of the volume of  $\text{CO}_2$  expired to the volume of  $\text{O}_2$  consumed. It has served for nearly a century as the basis for determining the relative participation of carbohydrates and fats in exercise [9,10].

$$\text{RQ} = \text{CO}_2/\text{O}_2$$

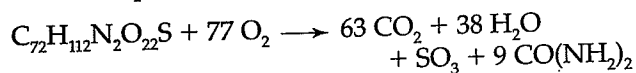
For carbohydrate catabolism, the RQ is 1:



For fat catabolism, the RQ is approximately 0.7:



The RQ for protein is about 0.82:



The amount of protein being oxidized can be estimated from the amount of urinary nitrogen produced, and the remainder of the metabolic energy must be a combination of carbohydrate and fat. Should the principal fuel source shift from mainly fat to carbohydrate, the RQ correspondingly increases, while a shift from carbohydrate to fat lowers the RQ. Tables exist that permit the estimation of the relative percentage of either carbohydrate or lipid being used as a metabolic fuel based on the RQ at any given time (for short-term exercise activities, it is often assumed that no amino acids are used for energy). During the past 20 years, however, such knowledge has been advanced by invasive techniques such as arteriovenous measurements and the use of needle biopsies to quantify tissue stores of the energy nutrients. These measurements are used clinically to evaluate elevated rates of metabolism. For examples, see the perspective "Nutrient Usage during Strenuous Exercise" at the end of Chapter 7.

The concept of maximum oxygen uptake is fundamental. As work increases in intensity, the volume of oxygen taken up by the body also increases. The  $\text{VO}_2$  max is defined as the point at which an increase in the intensity of the exercise no longer results in an increase in the volume of oxygen uptake. The intensity level of a particular workload is most commonly expressed in terms of the percentage of the  $\text{VO}_2$  max that it induces. As we discuss later, the metabolic pathway that supplies energy for work is determined by the availability

of metabolic energy (carbohydrate or lipid) and oxygen as well as by the duration of the activity and the conditioned state of the individual performing the work.

Isotope infusion can be used to quantify the contribution of the major energy substrates, plasma glucose and fatty acids, and muscle triacylglycerols and glycogen to energy expenditure during exercise. It involves the intravenous infusion of stable isotope (e.g.,  $^2\text{H}$  (deuterium))-labeled glucose, palmitate, and glycerol during periods of rest and exercise. By monitoring the uptake of infused labeled glucose and palmitate and knowing whole-body substrate oxidation, the contribution of muscle triacylglycerol and glycogen to overall energy supply can be estimated [8].

### Energy Sources during Exercise

The hydrolysis of the terminal phosphate group of ATP ultimately provides the energy for conducting biological work. In terms of physical performance, the form of work that is of greatest interest is the mechanical contraction of skeletal muscles. It is obvious, therefore, that physical exertion depends on a reservoir of ATP, which is in an ever-changing state of metabolic turnover. Whereas ATP is consumed by physical exertion, its stores are supplemented by the metabolic pathway discussed next and are repleted during periods of rest. The key to optimizing physical performance lies in nutritional strategies that maximize cellular levels of stored nutrients as fuels for ATP production. Three energy systems supply ATP during different forms of exercise [10]:

- the ATP-CP (creatine phosphate) system,
- the lactic acid system (anaerobic), and
- the aerobic system.

#### The ATP-CP (Phosphagen) System

The ATP-CP system is a cooperative system in muscle cells utilizing the high-energy phosphate bond of creatine phosphate (CP) together with ATP. When the body is at rest, energy needs are fulfilled by aerobic catabolism (see the section "The Aerobic System," below) because the low demand for oxygen can easily be met by oxygen exchange in the lungs and by the oxygen carried to the muscle by the cardiovascular system. (The ATP-CP system also operates continuously during this time, though at a slow pace). If physical activity is initiated, the energy requirements of contracting muscle are met by existing ATP. However, stores of ATP in muscle are limited, providing enough energy for only a few seconds of maximal exercise. As ATP levels diminish, they are replenished by the transfer of high-energy phosphate from creatine phosphate (CP) to form ATP in the ATP-CP system. The muscle cell concentration of CP is only four to five times greater than that of ATP, and therefore all



energy furnished by this system is expended after approximately 10 to 25 seconds of strenuous exercise. When the ATP-CP is expended, the lactic acid system kicks in to produce more ATP. Performance demands of high intensity and short duration such as weightlifting, 100-m sprinting, some positions in football, and various short-duration field events benefit most from the ATP-CP system. Lower-intensity activity may allow a person to use this system for up to 3 minutes.

### The Lactic Acid System

This system involves the glycolytic pathway by which ATP is produced in skeletal muscle by the incomplete breakdown of glucose anaerobically into 2 mol of lactate. The source of glucose is primarily muscle glycogen and, to a lesser extent, circulating glucose, and the lactic acid system can generate ATP quickly for high-intensity exercise. The lactate system is not efficient from the standpoint of the quantity of ATP produced. However, because the process is so rapid, the small amount of ATP is produced quickly and absolutely by substrate-level phosphorylation of ADP (Chap. 3). The lactate produced by this system quickly crosses the muscle cell membrane into the bloodstream, from which it can be cleared by other tissues (primarily the liver) for aerobic production of ATP or gluconeogenesis. In the event that the rate of production of lactate exceeds its clearance rate, blood lactic acid accumulates. This lowers the pH of the blood and is one cause of fatigue. Other factors of fatigue include a combination of lactate build-up and the lowering of pH. Under such circumstances, exercise cannot be continued for long periods. The lactic acid system is engaged to provide a rapid source of energy. When an inadequate supply of oxygen prevents the aerobic system from furnishing sufficient ATP to meet the demands of exercise, the lactic acid system will continue to function. Although the system is operative upon the onset of strenuous exercise, it becomes the primary supplier of energy only after the depletion of CP stores in the muscle. As a backup to the ATP-CP system, the lactic acid system becomes very important in high-intensity anaerobic power events lasting from 20 seconds to a few minutes, for example, longer sprints of up to 800 m and swimming events of 100 or 200 m.

### The Aerobic System

This system involves the Krebs cycle, through which carbohydrates, fats, and possibly amino acids are completely oxidized to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . The system, which requires oxygen, is highly efficient from the standpoint of the quantity of ATP produced. Because oxygen is necessary for the system to function, an individual's  $\text{VO}_2$  max becomes an important factor in his or her per-

formance capacity. Contributing to the  $\text{VO}_2$  max are the cardiovascular system's ability to deliver blood (which carries the oxygen) to exercising muscle, pulmonary ventilation, oxygenation of blood, and the utilization of the oxygen by skeletal muscle mitochondria. Matching these contributors to the cellular need for oxygen in exercising muscle is complex because a low efficiency of any of them becomes rate limiting for the entire process. In terms of cellular metabolism, the aerobic pathway is slow to become activated and begins to dominate the course of activity only after about 5 minutes of continuous activity. The aerobic system is an important supplier of energy for forms of exercise lasting longer than 3 or 4 minutes, depending on the intensity of the exercise. Both intracellular triacylglycerols and plasma fatty acids also contribute to the overall energy supply. Many types of exercise or sports meet these criteria, for example, distance running and swimming and cross-country skiing, just a few of the so-called endurance feats.

Current thinking is that the three energy systems do not simply take turns serially and that a particular system is not skipped in meeting the demands of exercise. Rather, all systems function at all times, and as one predominates the others participate to varying degrees (see the perspective "Nutrient Usage during Strenuous Exercise"). The interaction of the three systems over the course of the first 2 minutes of exercise is complex but appears to involve the following energy contributions:

- ATP-CP decreasing from most contributory to least contributory during the period;
- lactic acid steady, with high contribution; and
- aerobic progressing from least to highest contribution during the period.

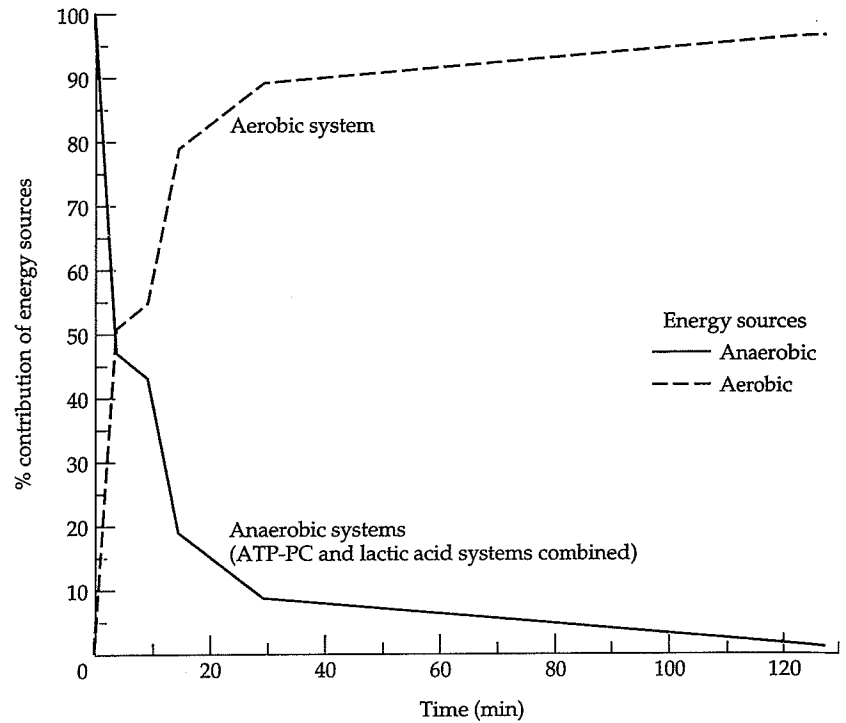
Energy contributions to long-term activity from aerobic and anaerobic systems are shown in Figure 8.11.

### Fuel Sources during Exercise

Carbohydrate, fat, and protein are the dietary sources that provide the fuel for energy transformation in the muscle. At rest, and during normal daily activities, fats are the primary source of energy, providing 80% to 90% of the energy. Carbohydrates provide 5% to 18% and protein 2% to 5% of energy during the resting state [11].

During exercise, the oxidation of amino acids contributes only minimally to the total amount of ATP used by working muscles. Significant breakdown of amino acids occurs only toward the end of a long endurance event, when carbohydrate (glycogen) stores are somewhat depleted. Amino acids can be transaminated to form alanine from pyruvate. The alanine is transported to the liver and is a primary substrate for gluconeogenesis.





**Figure 8.11** Primary energy sources for long-duration activity. *Source:* Adapted from Fox EL, Bowers RW, Foss ML. *The Physiological Basis for Exercise and Sports*, 3rd ed. Dubuque, IA: Brown and Benchmark, 1989, p. 37. Reproduced with permission of The McGraw-Hill Companies.

The carbon skeleton of some amino acids can be oxidized directly in the muscle. The four major endogenous sources of energy during exercise are

- muscle glycogen,
- plasma glucose,
- plasma fatty acids, and
- intramuscular triacylglycerols.

The extent to which each of these substrates contributes energy for exercise depends on several factors, including

- the intensity and duration of exercise,
- the level of exercise training,
- initial muscle glycogen levels, and
- supplementation with carbohydrates through the intestinal tract during exercise.

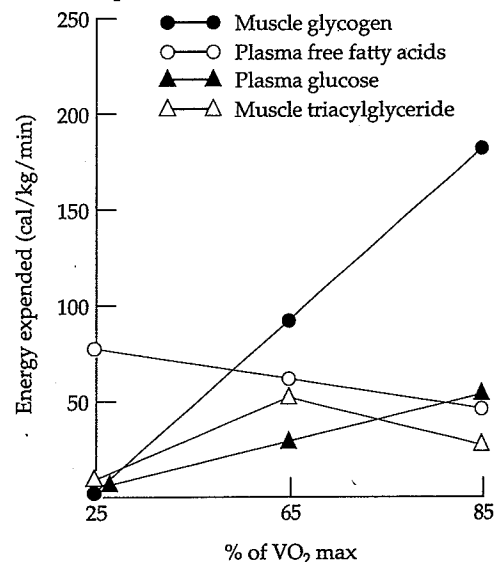
We will discuss the relationship between these factors and the “substrate of choice” for energy supply. A graphical representation of the contribution of these substrates at 25%, 65%, and 85%  $\text{VO}_2$  max is shown in Figure 8.12.

### Exercise Intensity and Duration

In the fasting state, much of the energy required for low-intensity levels of exercise (25%–30%  $\text{VO}_2$  max) is derived from muscle triacylglycerols and plasma fatty

acid oxidation, with a small contribution from plasma glucose. The pattern does not change significantly over a period of up to 2 hours at this exercise level, which is equivalent to walking. During this time, the consumed plasma fatty acids are replaced by mobilization of fatty acids from the large triacylglycerol stores in adipocytes throughout the body. However, as exercise intensity

**Figure 8.12** Contribution of the four major substrates to energy expenditure after 30 minutes of exercise at 25%, 65%, and 85%  $\text{VO}_2$  max.



increases to 65% and on up to 85%  $\text{VO}_2$  max, the release of adipocyte fatty acids into the plasma is reduced, resulting in a decrease in the concentration of plasma fatty acids. This decrease occurs despite a continuing high rate of lipolysis in adipocytes. The decreased replacement of plasma fatty acids from fat stores at higher levels of exercise has been attributed to insufficient blood flow and albumin delivery of fatty acids from adipose tissue into the systemic circulation [12]. Therefore, we would predict that fatty acids become trapped in adipose tissue and accumulate there during high levels of exercise, a theory supported by research [8].

With moderate-intensity exercise (~65%  $\text{VO}_2$  max) equivalent to running for 1 to 3 hours, total fat oxidation increases despite the reduced rate of return of adipose fatty acids into the circulation. This is attributed to an increase in the oxidation of muscle triacylglycerols. In fact, as shown in Figure 8.12, plasma fatty acids and muscle triacylglycerols contribute equally to energy expenditure at this level of exertion in endurance-trained athletes. Within the exertion range of 60% to 75%  $\text{VO}_2$  max, however, fat cannot be oxidized at a rate sufficiently high to provide needed energy, and therefore nearly half of the required energy must be furnished by carbohydrate oxidation. Note that fatty acids have only two oxygen molecules compared to an equal number of oxygen and carbon molecules in carbohydrates. This means that fatty acids require more oxygen to be delivered by the cardiovascular system. Also, the transfer of fatty acids into mitochondria is slow, and this may be a rate-limiting event. The result is that when tissue oxygen levels begin to be low and/or high-intensity exercise calls for a large quantity of energy, carbohydrate becomes a more favored substrate. Fatty acids are the favored substrates for intensities of up to about 50%  $\text{VO}_2$  max.

As exercise intensity increases to 85%  $\text{VO}_2$  max, the relative contribution of carbohydrate oxidation to total metabolism increases sharply (see Fig. 8.12). At  $\text{VO}_2$  max, carbohydrate in the form of blood glucose (derived from glycogenolysis of hepatic glycogen stores) and muscle glycogen essentially become the sole suppliers of energy. Like muscle glycogen, the concentration of blood glucose falls progressively during prolonged, strenuous exercise. This is due to the fact that glucose uptake by working muscle (independent of insulin) may increase to as much as 20-fold or more above resting levels, while hepatic glucose output decreases with exercise duration. Interestingly, however, hypoglycemia is not always observed at exhaustion, particularly at exercise intensities >70%  $\text{VO}_2$  max. Hypoglycemia following liver glycogen depletion apparently can be postponed by an inhibition of glucose uptake and accelerated gluconeogenesis in the liver,

using the glycerol produced in lipolysis, and by lactate and pyruvate produced by the glycolytic activity of the working muscles.

Accompanying high rates of carbohydrate catabolism is a rise in the production of lactic acid, which accumulates in muscle and blood. This is particularly evident in situations of oxygen debt, in which insufficient oxygen to complete the oxidation of pyruvate to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  instead favors its reduction to lactate.

The essentiality of carbohydrate as an energy substrate at moderate to high levels of exercise is due to the need for Krebs cycle intermediates from carbohydrates to oxidize the fatty acids, the slow rate of fat oxidation, and the limited ability of muscle to oxidize fat. Muscle fatigue occurs when the supply of glucose is inadequate, such as occurs with muscle glycogen depletion or hypoglycemia. To prevent this from happening, the individual must reduce workload intensity to a level that matches his or her ability to oxidize fat predominantly, possibly as low as 30%  $\text{VO}_2$  max. The reason for this limitation, and thus the dependence of muscle on carbohydrate as an energy source, is not fully understood. However, traditional thinking is that the limitation may be based on two factors: (1) oxidation of fatty acids is limited by the enzyme carnitine acyltransferase (CAT), which catalyzes the transport of fatty acids across the mitochondrial membrane; (2) CAT is known to be inhibited by malonyl CoA. When availability of carbohydrate to the muscle is high, fatty acid oxidation may be reduced by the inhibition of CAT by glucose-derived malonyl CoA [13].

### Level of Exercise Training

Endurance training increases an athlete's ability to perform more aerobically at the same absolute exercise intensity. Several factors aid in this. Endurance-trained muscle exhibits an increase in the number and size of mitochondria as well as an increase in cardiovascular capacity, lung capacity, and hypertrophy of the Type I muscle. The activity of oxidative enzymes in endurance-trained subjects has been shown to be 100% greater than in untrained subjects at 65%  $\text{VO}_2$  max. Endurance training also results in an increased utilization of fat as an energy source during submaximal exercise. In skeletal muscle, fatty acid oxidation has an inhibitory effect on glucose uptake and glycolysis. For this reason, the trained athlete benefits from the carbohydrate-sparing effect of enhanced fatty acid oxidation during competition because of slower depletion of muscle glycogen and plasma glucose. This largely accounts for the training-induced increase in endurance for exercise over a prolonged period.

It has been reported that trained individuals have a lower plasma fatty acid concentration and reduced

adipose tissue lipolysis compared to untrained counterparts at similar exercise intensity. This suggests that the primary source of fatty acids used by the trained individual is intramuscular triacylglycerol stores rather than adipocyte triacylglycerols. After a period of exercise, the intramuscular triacylglycerols are replaced with the fatty acids coming from plasma. Lipolysis from adipocytes increases the free fatty acid levels in plasma.

Endurance training appears to result in an increased capacity for muscle glycogen storage. Therefore, the trained athlete benefits not only from a slower utilization of muscle glycogen (as explained earlier) but also from the capacity to have higher glycogen stores at the onset of competition.

### Initial Muscle Glycogen Levels

The ability to sustain prolonged moderate to heavy exercise is largely dependent on the initial content of skeletal muscle glycogen, and the depletion of muscle glycogen is the single most consistently observed factor contributing to fatigue. High muscle glycogen levels allow exercise to continue longer at a submaximal workload. Even in the absence of carbohydrate loading (see the following section), a strong positive correlation exists between initial glycogen level and time to exhaustion and/or level of performance during exercise periods lasting more than 1 hour. The correlation does not apply at low levels of exertion (25%–35%  $\text{VO}_2$  max) or at high levels of exertion for short time periods because glycogen depletion is not a limiting factor under these conditions. It has been suggested that the importance of initial muscle glycogen stores is related to the inability of glucose and fatty acids to cross the cell membrane rapidly enough to provide adequate substrate for mitochondrial respiration [14].

### Carbohydrate Supplementation (Supercompensation)

When muscle glycogen was identified as the limiting factor for the capacity to exercise at intensities requiring 70% to 85%  $\text{VO}_2$  max, dietary manipulation to maximize glycogen stores followed naturally. The most popular subject for research of this nature has been the marathon runner or cross-country skier because of the prolonged physical taxation of these events and the fact that the athlete's performance is readily measurable by the time required to complete the course. The major dietary concern to emerge in the endurance training of marathon runners was how to elevate muscle glycogen to above-normal (supercompensated) levels. In sporting vernacular, maximizing glycogen content by dietary manipulation is referred to as "carbohydrate loading."

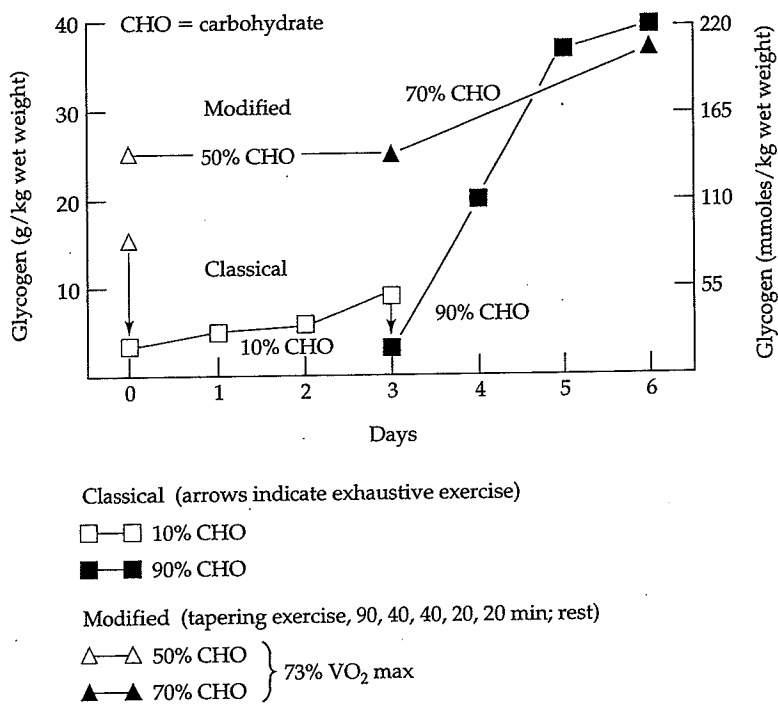
The so-called classical regimen for carbohydrate loading resulted from investigations in the late 1960s by

Scandinavian scientists [15]. This regimen involved two sessions of intense exercise to exhaustion to deplete muscle glycogen stores separated by 2 days of low-carbohydrate diet (<10%) to "starve" the muscle of carbohydrate. This was followed by 3 days of high-carbohydrate diet (>90%) and rest. The event would be performed on day 7 of the regimen. On completion of this regimen, muscle glycogen levels approached 220 mmol/kg wet weight (expressed as glucose residues), more than double the athlete's resting level. However, because of various undesirable side effects of the classical regimen, such as irritability, dizziness, and a diminished exercise capacity, a less stringent regimen of diet and exercise has evolved that produces comparably high muscle glycogen levels.

In the modified regimen, runners perform "tapered-down" exercise sessions over the course of 5 days, followed by 1 day of rest. During this time, 3 days of a 50% carbohydrate diet are followed by 3 days of a 70% carbohydrate diet, generally achieved by consuming large quantities of pasta and rice or bread. The modified regimen, which can increase muscle glycogen stores 20% to 40% above normal, has been shown to be as effective as the classical approach with fewer adverse side effects.

Figure 8.13 illustrates graphically the amount of muscle glycogen formed as a result of each regimen. Predictably, the supercompensation of muscle glycogen by either approach has been shown to improve performance in trained runners during races of 30 km and longer. It did not improve performance in shorter races (<21 km) owing to the fact that glycogen depletion is not the limiting factor in such events. Other nutritional factors involving carbohydrate intake may enhance performance, as discussed next.

**Preevent Meal.** The timing of the final meal before intense exercise is crucial, because fasting results in a reduction of the labile glycogen stores of liver, while carbohydrate meals consumed too close in time to the event may cause **hyperinsulinemia**. Stimulation of insulin release just before an event results in a rapid reduction in plasma glucose, significantly impairing work capacity. Exercise permits a rapid uptake of glucose by the muscle in addition to the insulin-stimulated uptake. Elevated plasma insulin also inhibits liver glucose output and the normal rise of plasma free fatty acids. Under such conditions, excessive muscle glycogen degradation occurs, resulting in early fatigue. The final meal before intense exercise should be consumed several hours before the event so that the stomach is empty and allows for rapid water absorption. For long endurance events, the meal generally should be high in complex carbohydrates and low in fat, conditions that



**Figure 8.13** Schematic representation of the “classical” regimen of muscle glycogen supercompensation described by Scandinavian investigators and the “modified” regimen of muscle glycogen supercompensation, which has been shown to elevate muscle glycogen stores to comparably high levels with “normal” diets and a “tapering-down” sequence of exercise. Source: From Sherman WM. Carbohydrate, muscle glycogen, and muscle glycogen supercompensation. In: *Ergogenic Aids in Sport*. by Williams MH, Champaign, IL: Human Kinetics Publishers, 1983, p. 14. Reprinted by permission.

promote rapid emptying of the stomach. The nature of the food consumed is up to the athlete.

An isotonic or hypotonic beverage containing carbohydrate 15 to 20 minutes prior to the event provides extra dietary glucose without stimulating insulin release. For prolonged events (longer than 90 minutes), the consumption of fluid containing some carbohydrate helps with fluid balance as well as with maintaining blood glucose (see Chap. 14). Balance must be maintained to allow the liquid to empty rapidly from the stomach and the carbohydrate to be rapidly absorbed. A full discussion of these factors is beyond the scope of this text. In brief, the beverage should be cool, not cold, be isotonic or hypotonic, and contain glucose or polyglucose. Large amounts of fructose should not be included because of its slow absorption rate.

**Glycemic Index.** The form of carbohydrate ingested is also an important consideration in optimizing endurance performance. The principal factor in this regard is the glycemic index (GI) of the food (see Chap. 4 for a full explanation of glycemic index). Potato starch is considered to have a relatively high GI, though not as high as the simple sugars. Generally, low to moderate GI carbohydrate loading prior to the performance is preferred to high GI carbohydrate intake because the hyperinsulinemic effect of the high GI food, as mentioned earlier, results in a rapid reduction in blood glucose, suppressed release of fatty acids from store, and inhibition of hepatic glycogenolysis.

After a prolonged event, the reverse is true with respect to the GI of foods consumed. Immediately after a glycogen-depleting event, liver and muscle glycogen levels are very low, and glycogen levels will recover faster if a high GI food or beverage is consumed. These foods can be as simple as wedges of orange or apple or one of the sports drinks containing glucose, sucrose, or polyglucose. Recovery depends on replacing lost body water, rebuilding glycogen levels, rebuilding lost muscle protein, and, for very long events, restoring electrolyte balance. This last topic will be covered in more detail in Chapter 14.

### Nutritional Ergogenic Aids

The word *ergogenic* is derived from the Greek word *ergon*, meaning “work,” and is defined as increasing work or the potential to do work. An ergogenic aid does not need to be nutritional; it can also be mechanical. For example, a running shoe or body suit to improve aerodynamics can be a mechanical ergogenic aid. We will limit this discussion to nutritional ergogenic supplements, or ergogenic aids. Often these are substances that are part of a normal diet, or they may be cellular metabolites that are ingested in an effort to enhance the capacity for sport, exercise, and physical performance. Several nutritional practices have ergogenic properties that are not necessarily considered ergogenic supplementation, for example, carbohydrate loading and fat loading. Fat loading has been purported to “spare” the more limited carbohydrates. As mentioned previously,

fats are the major fuel source for exercise below 50%  $\text{VO}_2$  max.

Nutritional ergogenic supplements are also to be distinguished from ergogenic drugs such as anabolic steroids or stimulants. The risks of using anabolic steroids are so great that they have prompted the enactment and enforcement of laws prohibiting their use in strength or endurance competitions. The compulsion for improved performance among athletes has led to an enormous increase in the testing and use of nutritional ergogenic aids. As expected, the literature dealing with the subject has expanded with equal zeal. Many supplements that have not been fully tested for either safety or efficacy have been recommended through the lay press. The information presented here will be restricted to the theoretical basis for their use and a brief overview of what is known about the effectiveness of ergogenic supplementation.

There appears to be a dichotomy between the widespread public use of certain supplements and the lack of scientific support for such use. A problem for researchers is the common perception of subjects under study that they simply "feel better" as a result of supplementation, even though actual physiological changes may not be documented by the research. In other words, psychological effects are adding a new dimension to the testing of ergogenic aids. These must be considered along with true physiological effects, because as mood and mental outlook improve, so does physical performance. This is the bottom line for using supplements in the first place. For all nutritional ergogenic aids, the placebo effect is significant. The level of athletic performance is influenced by psychological factors. By "believing" that a certain supplement will make you perform better, you may actually perform better. Often there is a theoretical "rationale" for supplement use, but it does not necessarily translate into enhancement of performance.

Following is a listing of micronutrient ergogenic supplements that have been consumed on a broad basis. The supplements chosen for citing were selected on the basis of their reputed efficacy from a much longer list of hit-or-miss trial substances. In most instances, research results neither totally support nor totally refute supplement efficacy but instead are divided in their findings. Reference occasionally will be made to the number of "pro and con" study conclusions to help the reader evaluate a substance's efficacy. Although specific references will not be included, they, along with many more pertinent sources of information, are available to the interested reader [16,17].

### Amino Acids

**Arginine.** Arginine has been shown to elicit the release of somatotropin with large oral doses. Somatotropin,

which has been referred to as insulin-like growth factor, stimulates protein synthesis.

**Ornithine.** Oral doses of ornithine have also been shown to stimulate the release of somatotropin. At the levels required, the side effect of osmotic diarrhea was often seen. Both arginine and ornithine are purported to be beneficial in resistance training.

**Aspartate Salts.** The potassium-magnesium salts of aspartate have been marketed as an antifatigue agent. Their use has been questioned, however, and the benefit is more likely a placebo effect. The aspartate salts may have some benefits in endurance events if taken in high doses. Time to exhaustion has been reported to be increased.

**Branched-Chain Amino Acids.** Branched-chained amino acids (isoleucine, leucine, and valine) have been hypothesized to benefit endurance activities by influencing the level of serum tryptophan. BCAAs compete with tryptophan for entry into the brain. One theory on fatigue is that brain tryptophan is converted to serotonin, which causes fatigue. This may be one of several factors bringing about fatigue. BCAAs are also used by muscle for energy near the end of very long endurance events. It has been suggested that consuming BCAAs prior to an event will provide energy toward the end of the event and thereby reduce the amount of muscle breakdown.

### Antioxidants

Endurance exercise increases the amount of oxygen moving into the muscle. Increased exposure to large volumes of oxygen in turn increases the generation of free radicals, which have been shown to be involved with fatigue and damage to the muscle cell membrane. This information provides the rationale for the use of antioxidants to prevent muscle damage and delay fatigue. Many antioxidants have been used, including vitamin C, vitamin E, and selenium. Coenzyme  $\text{Q}_{10}$  also has antioxidant activity, though its use as an ergogenic aid is based on other properties.

### Herbs

Much interest has recently been directed toward herbal preparations. It is difficult to evaluate and compare studies on these preparations because their collection, processing, and agricultural growing conditions influence the active components. One class of herbals, ephedra, was previously used for its ephedrine content. The risk of harmful side effects or death has discouraged its use and caused it to be banned from use by athletes in most sports.

**The Ginsengs.** The most widely used and studied herbs are the ginsengs. Some purported ergogenic benefits of *Panax* (Chinese/Korean) ginseng include

- increased run time to exhaustion (three out of seven studies),
- increased muscle strength (one out of two studies),
- improved recovery from exercise (three out of four studies),
- improved oxygen metabolism during exercise (seven out of nine studies),
- reduced exercise-induced lactate (five out of nine studies),
- improved auditory and visual reaction times (six out of seven studies), and
- improved vitality and feelings of well-being (six out of nine studies).

These benefits have more consistently been reported following supplementation over more than 8 weeks [18].

### Caffeine

Ergogenic effects of caffeine are seen in endurance events. It is generally recognized that the largest impact is seen in individuals who do not consume caffeine on a regular basis. Caffeine is a CNS stimulant, increasing blood flow to the kidneys (thus acting as a diuretic) and stimulating the release of fatty acids from adipose. Sport regulatory bodies have set an upper limit for the permissible level of caffeine consumption.

### Intermediary Metabolites

**Bicarbonate.** Bicarbonate is a primary buffering agent in the body. Athletes competing in short anaerobic events (lasting only a few minutes) build up lactic acid. The lowering of blood pH is one factor leading to fatigue. Theoretically, loading with sodium bicarbonate would delay the drop in pH and thereby delay fatigue. Studies have supported this benefit, and it is often mentioned in reviews of ergogenic aids. In conversations with many sprint athletes and coaches, however, none reported having used sodium bicarbonate, nor did they know of anyone who did.

**Carnitine.** L-carnitine is used by the body to transfer acyl CoA from the cytoplasm of a cell into the mitochondria. This is the theoretical basis for the use of carnitine as a nutritional ergogenic aid. In indi-

viduals fed parenterally for long periods of time, it has been shown that fatty acid utilization can be enhanced by supplementation with carnitine. Individuals with chronic cardiovascular disease have also been shown to benefit from carnitine. For the athlete, studies that show benefit and those that do not are about even.

**Coenzyme Q<sub>10</sub>.** The theoretical basis for coenzyme Q<sub>10</sub> as an ergogenic aid stems from its pivotal role in electron transport and production of ATP in the mitochondrion. Clinical studies have shown its safety and use in cardiovascular disease. Supplementation with coenzyme Q<sub>10</sub> longer than 4 weeks has been purported to provide benefits for the long-term endurance athlete. This benefit has not been shown conclusively, however.

**Creatine.** Muscle creatine is part of the ATP-CP energy system that supplies the initial energy during the first few seconds to minutes of exercise. The theoretical basis for using creatine as a nutritional ergogenic aid is that the saturation of muscle with creatine increases the amount of creatine phosphate in the muscle. Creatine has been shown to be effective for short, intense exercise. However, there are associated risks in taking it. Individuals taking creatine appear to add 1 to 2 kg of water weight. Those taking creatine in hot, humid environments have become dehydrated and more susceptible to heat stress. Deaths have been reported.

**Other.** Many other nutritional materials have been recommended in the lay literature as possessing ergogenic properties, including minerals such as calcium, magnesium, zinc, iron, phosphates, chromium, boron, and vanadium and most vitamins. Reviews of mineral supplements [16] suggest that performance enhancement is not well established and that the major benefit of mineral supplementation lies in the correction of deficiencies should they exist.

General problems of research design remain as the popularity of nutritional ergogenic supplements surges forward. As indicated previously, many ergogenic effects may be attributed to mental and psychological changes, and it behooves future researchers to rule these out in an effort to establish strictly physiological effects. The fact that the number of studies finding "for" performance enhancement is nearly equaled by the number of those finding "against" enhancement testifies to the difficulty involved in researching this important field.

## summary

**A**nimal survival depends on a constant internal environment maintained through specific control mechanisms. Controls, operative at all levels (cellular, organ, and system), integrate energy metabolism and allow the body to adapt to a wide variety of environmental conditions. Primary among the mechanisms of adaptation is the regulation of metabolism through the cooperative input of the nervous, endocrine, and vascular systems. In the normal operation of these systems, metabolic pathways may be stimulated, maintained, or inhibited, depending on the conditions imposed on the body. A pointed example of metabolic adaptation is the shift that occurs in substrate utilization and metabolic pathways in answer to changes in the body's nourishment status (i.e., fed, fasting, and starvation states).

The physical stress of exercise and sport presents an interesting challenge to the regulatory capacity of the body to provide the additional energy needed by the exercising muscles. Substrates fueling this energy include plasma free fatty acids, plasma glucose, muscle glycogen, and muscle triacylglycerols, and their utilization varies according to the intensity and duration of the exercise. Many substances have been tested for their ergogenic properties in attempts to improve performance in high-intensity and endurance sports. In most cases, test results remain controversial, and more research is needed to establish which of the reputed ergogenic aids produce true physiological improvement.

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## Suggested Readings

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Harris RA, Crabb DW. Metabolic interrelationships. In: Devlin TM, ed. *Textbook of Biochemistry with Clinical Correlations*, 3rd ed. New York: Wiley, 1992, pp. 576-606. This integration of human metabolic pathways is written primarily for the medical student. Information is presented so as to be relevant for the health practitioner.

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Wolinsky I. *Nutrition in Exercise and Sport*, 3rd ed. Boca Raton: CRC Press, 1998. A thorough treatment of what is known and what is not in sports nutrition.

## Web Sites

- [www.nal.usda.gov/fnic/pubs/bibs/gen/97-sp-hp.htm](http://www.nal.usda.gov/fnic/pubs/bibs/gen/97-sp-hp.htm)  
National Agricultural Library: Sports Nutrition Resource List for Health Professionals
- [www.umass.edu/cnshp/index.html](http://www.umass.edu/cnshp/index.html)  
Center for Nutrition in Sport and Human Performance at the University of Massachusetts
- [www.faseb.org/ajcn](http://www.faseb.org/ajcn)  
*American Journal of Clinical Nutrition*
- [www.gssiweb.com/](http://www.gssiweb.com/)  
Gatorade Sports Science Institute



## Diabetes: Metabolism Out of Control

**D**iabetes mellitus, the disease characterized by the body's inability to metabolize glucose, manifests as one of two types: type 1, or insulin-dependent diabetes mellitus, ketosis prone (IDDM); and type 2, non-insulin-dependent diabetes mellitus (NIDDM). The long-term consequences of diabetes demonstrate that lipid metabolism is also involved. The two types are mechanistically very different and will be discussed separately. Current theories on the etiology and characteristics of these two classifications of diabetes are shown in Figure 1.

### Non-Insulin-Dependent Diabetes Mellitus (Type 2)

Type 2 diabetes accounts for 80% to 90% of all reported cases of the disease. The cause of type 2 diabetes has not been completely resolved, but it appears to be associated with insulin resistance in peripheral target tissue. This condition is caused not by a failure of

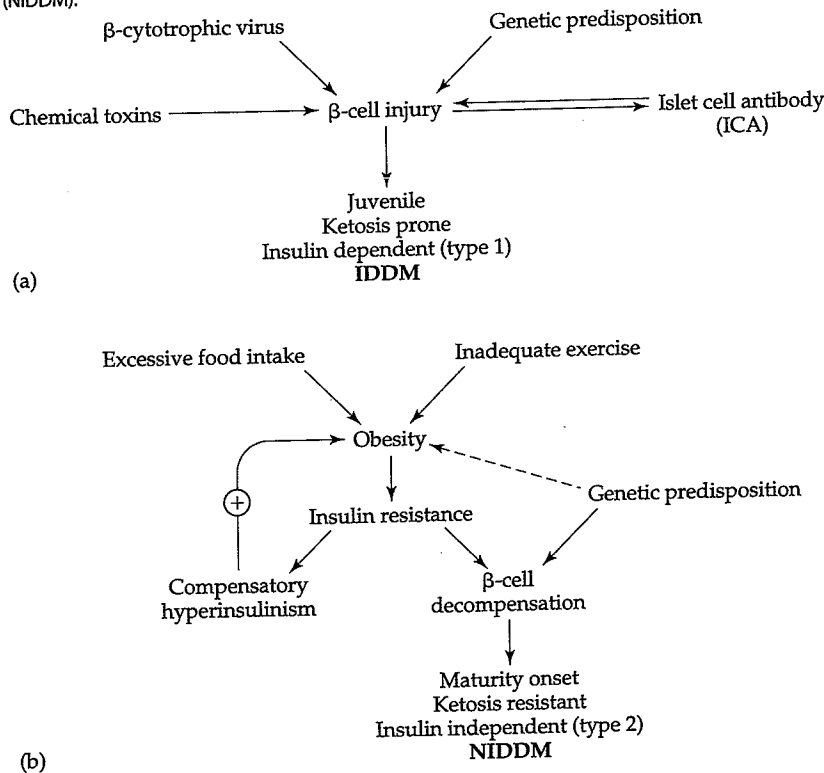
target cells to bind insulin but by a postbinding abnormality, arising somewhere in the sequence of events that follows the binding of insulin to its receptor and leads to the cell's normal response to that signal. Experimental evidence suggests that a primary cause for the interrupted insulin signal may be compromised synthesis or mobilization of the cell's glucose transporters (refer to the section "Glucose Transporters," Chap. 4).

In skeletal muscle cells, insulin resistance associated with NIDDM has been shown to be caused by a reduction in glucose transporter activity, specifically the failure of the vesicles to translocate in response to insulin (see Fig. 4.8). The error can be thought of as a block or short-circuit in the insulin signal that normally initiates the translocation process. The result is a reduced concentration of transporters at the cell surface and a consequent reduction in the rate of glucose uptake. Although a similar defect was found in adipocytes of NIDDM patients, it

is not the major cause of the insulin resistance in these cells. Rather, the consequence of NIDDM in adipocytes is a marked depletion of mRNA encoding the GLUT4 transporter, resulting in depleted intracellular stores of the protein [1]. This describes a pretranslational defect, meaning that it interferes with protein synthesis at a level before the translation process, the step that requires mRNA as template. Therefore, even if the vesicle translocation process were not compromised, an inadequate number of surface receptors would still be expressed upon insulin stimulation.

Insulin resistance has also been described in obesity as well as in NIDDM. Insulin resistance in obesity is mechanistically similar to the NIDDM effect on adipocytes. Reduction in GLUT4 mRNA in obese subjects results in a decrease in de novo synthesis of the transporter. Furthermore, the extent to which mRNA expression is suppressed appears to relate directly to increasing adiposity.

**Figure 1** Overview of present theories of diabetes mellitus etiology. (a) depicts the factors impinging on the development of diabetes mellitus that requires exogenous insulin. This type of diabetes presently is most commonly designated as insulin-dependent diabetes mellitus (IDDM). (b) illustrates the interaction of factors that may result in non-insulin-dependent diabetes mellitus (NIDDM).







The ketonuria along with glucosuria associated with acidosis causes an excessive loss of sodium from the body, and loss of this extracellular cation further compromises body water balance. A net loss of potassium, the chief intracellular cation, accompanies increased protein catabolism and cellular dehydration, both of which characterize uncontrolled diabetes.

The normal flow of substrates following food intake, as depicted in Figure 8.7, is

largely dependent on the secretion of insulin. Insulin exerts a potent, positive effect on anabolism, emphasized in the figure, while inhibiting catabolic pathways. Figure 2, in contrast, shows metabolism out of control when the inhibiting effect of insulin is lacking and conservation of energy is impossible. Diabetes is a vivid negative example of the integration of metabolism and the importance of metabolic regulation (homeostasis) to continuance of life.

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**Web Sites**

- [www.diabetes.org](http://www.diabetes.org)  
American Diabetes Association
- [www.jdfcure.org](http://www.jdfcure.org)  
Juvenile Diabetes Foundation