CHAPTER 3

THE MAINTENANCE OF ATP HOMEOSTASIS IN ENERGETICS AND HUMAN MOVEMENT

All forms of human movement, including athletic, occupational, and rehabilitation exercises, can be described as energetic events, with the liberation and harnessing of energy central to performance. Adenosine triphosphate (ATP, Chapter 2) is the common chemical intermediate used to power muscle contractions and other forms of cell work. Cell, tissue, and organ systems are designed to maintain constant cellular ATP concentrations [ATP] over wide ranges of use (turnover rates). Constancy of [ATP] over wide variations of turnover is referred to as **ATP homeostasis.**

Athletic activities can be classified as one of three groups: power, speed, and endurance events (see Table 3-1). Examples of these groups are the shot put, the 400-m sprint, and the marathon run, respectively. Success in each of these events depends largely on energetics and the biochemical mechanisms supporting ATP homeostasis. Skeletal muscle has three energy systems, each of which is used in these three types of activities. In power events, where the activity lasts a few seconds or less, the muscle has several immediate energy sources (Figure 3-2). For rapid, forceful exercises lasting from a few seconds to approximately 1 minute, muscle depends mainly on nonoxidative, or glycolytic, energy sources, as well as on immediate sources. For activities lasting 2 minutes or more, oxidative mechanisms become increasingly important. Before

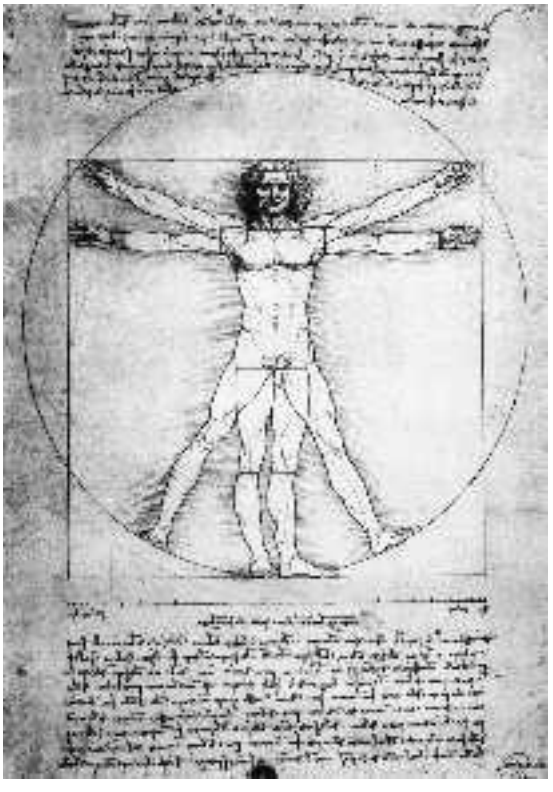

Figure 3-1 Leonardo's drawing of man's ability to move represents the fact that the laws of nature operate to control and limit human muscular performance. SOURCE: © Corbis/Bettman.

TABLE 3-1

Energy Sources of Muscular Work for Different Types of Activities

	Power	Speed	Endurance
Duration of event	0 to 3 sec	4 to 50 sec	>2 min
Example of event	Shot put, discus, weight lifting	100- to 400-m run	≥1500-m run
Enzyme system	Single enzyme	One complex pathway	Several complex pathways
Enzyme location	Cytosol	Cytosol	Cytosol and mitochondria
Fuel storage site	Cytosol	Cytosol	Cytosol, blood, liver, adipose tissue
Rate of process	Immediate, very rapid	Rapid	Slower but prolonged
Storage form	ATP, creatine phosphate	Muscle glycogen and glucose	Muscle and liver glycogen, glucose; muscle, blood, and adipose tissue lipids; muscle, blood, and liver amino acids
Oxygen involved	No	No	Yes

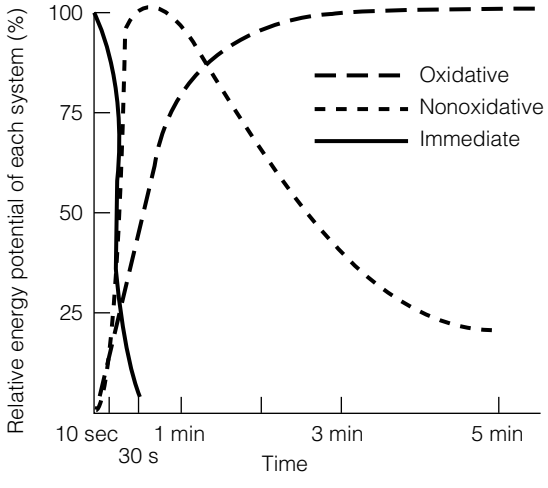

Figure 3-2 Energy sources for muscle as a function of activity duration. Schematic presentation showing how long each of the major energy systems can endure in supporting all-out work. SOURCE: D. W. Edington and V. R. Edgerton, 1976. Used with permission.

describing these three basic muscle energy sources, we need to describe the chemical-mechanical energy transduction of smuscle contraction, as depicted in Equation 3-1.

In this reaction, actin and myosin are the two contractile proteins of muscle, and Ca^{2+} is the calcium ion whose presence triggers the combination of actin and myosin. Inorganic phosphate (P_i) is also produced by the reaction.

■ Immediate Energy Sources

Each of the three main energy sources in support of ATP homeostasis in muscle is mediated by specific enzymes or enzyme systems, as described in Tables 3-1 and 3-2. In any muscle contraction, whether the activity is primarily one of power or endurance, the degradation of ATP supplies the chemical energy to power the contraction (Eq. 3-1).

The immediate energy source in muscle, as in most other cells, is composed of three components. First, there is ATP itself. ATP is degraded by enzymes that are generally called ATPases. Because the reaction involves combination with H_2O, the splitting of ATP is called hydrolysis (Eq. 3-2).

The chemical products of ATP hydrolysis are adenosine diphosphate (ADP) and inorganic phosphate (P_i). In the cyclic process of muscle contraction

$$\text{ATP} + \text{Actin} + \text{Myosin} \xrightarrow{Ca^{2+}} \text{Actomyosin} + P_i + \text{ADP} + \text{Energy (heat + work)} \quad (3\text{-}1)$$

$$\text{ATP} + H_2O \xrightarrow{\text{ATPase}} \text{ADP} + P_i \quad (3\text{-}2)$$

TABLE 3-2

Estimation of the Energy Available in the Body Through Immediate (Phosphagen) Energy Sources

	ATP	CP	Myokinase ATP Equivalent	Total Phosphagen (ATP + CP)
Muscular concentration				
mmol · kg^{-1} muscle[a]	6	28		34
mmol total muscle mass[b]	180	840	90	1110
Useful energy[c]				
kcal · kg^{-1} muscle	0.06	0.28		0.34
kcal total muscle mass	1.8	8.4	0.9	11.1

[a]Based on data from Edwards et al., 1982.
[b]Assuming 30 kg of muscle in a 70-kg man.
[c]Assuming 10 kcal · mol^{-1} ATP.

and recovery from contraction, ATP is continually being hydrolyzed to ADP, and ADP is continually being reenergized by phosphorylation back to ATP.

The standard free energy of hydrolysis ($\Delta G°'$) of ATP measured under test tube conditions is -7.3 kcal · mol^{-1}. In the body, however, the actual free energy of ATP hydrolysis (i.e., the ΔG) is probably closer to -11 kcal · mol^{-1} (Chapter 2). This is because conditions in the living cell are somewhat different from standard test tube conditions, and more energy is available from ATP splitting in our muscles than in test tubes under standard conditions.

The second cellular source of immediate energy is creatine phosphate (CP). This high-energy phosphorylated compound exists in five to six times greater concentration in resting muscle than does ATP. Creatine phosphate provides a reserve of phosphate energy to regenerate ATP, which is consumed as the result of muscle contraction. The interaction of CP and ADP (degraded ATP) is catalyzed by the enzyme *creatine kinase,* an enzyme with a very low K_M and a very high V_{max} (for definitions, see below).

$$\text{CP} + \text{ADP} \xrightarrow[\text{kinase}]{\text{Creatine}} \text{ATP} + \text{C} \qquad (3\text{-}3)$$

Thus, in the muscle, ATP that is hydrolyzed to ADP during muscle contraction is rephosphorylated by CP. Seen in this role, CP is particularly important as an intracellular energy shuttle. This is discussed more in Chapter 6. Here it is sufficient to note that hydrolysis of ATP by the contractile apparatus in muscle is rapidly compensated for by cytoplasmic creatine kinase and creatine phosphate stores. The resulting creatine is then rephosphorylated through the action of mitochondrial creatine kinase, which accesses mitochondrial ATP.

The third immediate energy source in muscle involves an enzyme called *adenylate kinase,* which in muscle is also referred to as *myokinase.* The enzyme has the ability to generate one ATP (and one AMP) from two ADPs. As already mentioned in Chapter 2, AMP is important because its presence is a profound signal for activating mechanisms of ADP restoration to ATP.

$$\text{ADP} + \text{ADP} \xrightarrow[\text{kinase}]{\text{Adenylate}} \text{ATP} + \text{AMP} \qquad (3\text{-}4)$$

The three components of the immediate energy system and the respective kinase enzymes in muscle are all H_2O-soluble. Therefore, they exist throughout the aqueous part of the cell, from near the cell's inner boundary to deep within it, surrounding the contractile elements, actin and myosin, and other important parts of the cell. The immediate energy sources are so named because they are immediately available to support muscle contraction.

Quantitatively, ATP and CP (which together are called *phosphagen*) make up a critical and important energy reserve. The amount of ATP on hand, however, cannot sustain maximal muscle contraction for more than a few seconds (Table 3-2). Even when ATP is augmented by both CP and the myokinase enzyme system, activities that must be sustained for more than a fraction of a minute (i.e., more than 5–15 seconds) require the assistance of other energy sources.

■ Nonoxidative (Glycolytic) Energy Sources

By convention, we use the terms *glycolytic* and *nonoxidative* interchangeably. Nonoxidative energy sources in muscle are the breakdowns of glucose (a simple sugar) and glycogen (stored carbohydrate made up of many glucose subunits). These processes are specifically termed *glycolysis* and *glycogenolysis*, respectively. Muscle tissue is densely packed with glycolytic and glycogenolytic enzymes; therefore, muscle is specialized in these processes and can break down glucose and glycogen rapidly, with the net formation of lactic acid, which dissociates to a lactate anion and proton at physiological pH. Glycolysis can be summarized as follows:

$$\text{Glucose} \xrightarrow[\text{Glycolysis}]{} 2\ \text{ATP} + 2\ \text{Lactate}^- + 2\text{H}^+ \qquad (3\text{-}5)$$

In skeletal muscle, the concentration of free glucose is very low, so most of the potential energy available from nonoxidative energy sources comes from the breakdown of glycogen (Table 3-3).

Like the immediate energy system, the nonoxidative energy system is composed of elements that are H_2O-soluble and exist in the cell cytosol. The apparatus for nonoxidative energy metabolism therefore exists in immediate proximity to the contractile elements in muscle. Nonoxidative energy sources are called upon when muscle contraction lasts more than a few seconds.

Quantitatively, the energy available through nonoxidative metabolism (Table 3-3) is significantly greater than that available through immediate energy sources (Table 3-2). However, immediate and nonoxidative energy sources combined still provide only a small fraction of the energy available through oxidative metabolism. Therefore, intense muscular activities lasting longer than approximately 30 seconds cannot be sustained without the benefit of oxidative metabolism (see Figure 3-2). As well, oxidative metabolism is necessary for recovery and restoration of immediate and nonoxidative energy systems after maximal-effort exercise stresses.

TABLE 3-3

Estimation of the Energy Available in the Body Through Nonoxidative (Glycolytic) Available in Metabolism

	Per Kilogram Muscle	Total Muscle Mass[a]
Maximal lactic acid tolerance (g)	3.0	90
ATP formation (mmol)	50.0	1500
Useful energy (kcal)	0.5	15

[a]Assumes that all muscles were activated simultaneously.

SOURCE: Based on data from Karlsson, 1971.

Before leaving this topic, it is important to note some new and very important results concerning the pathways of glycolytic and oxidative metabolism and their linkage. As will be discussed in Chapter 6, glycolysis inevitably results in lactate formation, with 10 or more times more lactate than pyruvate present in resting muscle and other tissues. However, while resting muscle releases lactate on a net basis, and working muscle can actually consume lactate on a net basis, lactate formation occurs continuously as a function of the glycolytic flux rate. But, because most lactate enters mitochondria and is oxidized within muscle cells and tissues, lactate formation through glycolysis and removal through oxidation are in balance. Consequently, while glycolysis inevitably results in lactate production, the accumulation and net release of lactate from muscle and other tissues is much less than the amount of lactate produced in muscle and other tissues. The production, distribution, and use of lactate (i.e., the lactate shuttle) represents an important means to link glycolytic and oxidative metabolism.

■ Oxidative Energy Sources

Potential oxidative energy sources for muscle include sugars, carbohydrates, fats, and particular amino acids. As just noted, muscle tissue in healthy, fed individuals has significant reserves of glycogen. This fuel source can be supplemented by glucose supplied from the blood; liver glycogen, which can be broken down to glucose and delivered to muscle through the circulation; and fats and amino acids, which exist in muscle as well as in other depots around the body. Further, whereas the sugar glucose can be metabolized to an extent by glycolytic mechanisms (Eq. 3-5), oxidative mechanisms allow far more energy to be liberated from a glucose molecule.

$$\text{Glucose} + O_2 \xrightarrow[\text{metabolism}]{\text{Oxidative}} 36\ \text{ATP} + CO_2 + H_2O \qquad (3\text{-}6)$$

The additional energy available from glucose degradation by oxidative (Eq. 3-6) compared to nonoxidative (Eq. 3-5) mechanisms is liberated because the oxidative pathways of metabolism carry on the process of glucose catabolism to a far greater extent than do the nonoxidative pathways. The oxidative breakdown of glucose is longer and more involved, so the opportunity for energy transduction and capture of glucose chemical energy in the form of ATP is greater. The details of oxidative metabolism will be discussed in more detail in Chapters 6, 7, and 8.

Fats can be catabolized by oxidative mechanisms only, but the energy yield is very large. For palmitate, an average-sized and commonly occurring fatty acid:

$$\text{Palmitate} + O_2 \xrightarrow[\text{metabolism}]{\text{Oxidative}} 129\ \text{ATP} + CO_2 + H_2O \qquad (3\text{-}7)$$

Like fats, amino acids can be catabolized only by oxidative mechanisms. Before an amino acid can be oxidized, the nitrogen residue must be removed.

TABLE 3-4

Estimation of Energy Available from Muscle and Liver Glycogen, Fat (Adipose Triglyceride), and Body Proteins

	Energy Equivalent (kcal)
Glycogen in muscle	480
Glycogen in liver	280
Fat (adipose triglyceride)	141,000
Body proteins	24,000

SOURCE: Based on data from Young and Scrimshaw, 1971.

This is generally done by switching the nitrogen to some other compound (a process called *transamination*) or by a unique process of nitrogen removal in the liver (oxidative deamination). Examples involving alanine, a three-carbon amino acid, are seen in Equations 3-8 and 3-9. Generally, amino acids are poor and less preferred energy sources for working muscle (Chapters 4 and 8).

The significance of oxidative metabolism for energy production in the body is illustrated in Table 3-4. In comparison to the energy potential of the immediate energy system (Table 3-2) and the nonoxidative metabolism of glycogen (Table 3-3), the energy available from oxidative energy sources is far greater. Also, the energy available from the combustion of muscle glycogen is small compared with the much larger potential energy reserves in fat and body protein.

■ Aerobic and Anaerobic Metabolism

Of the body's three energy systems, two systems (the immediate and nonoxidative) do not require oxygen for their operation. Consequently, by convention these systems are referred to as *anaerobic,*

$$\text{Alanine} + \alpha\text{-Ketoglutarate} \xrightarrow[\text{pyruvate transaminase}]{\text{Glutamate}} \text{Pyruvate} + \text{Glutamate} \qquad (3\text{-}8)$$

$$\text{Pyruvate} + O_2 \xrightarrow[\text{metabolism}]{\text{Oxidative}} 15\ \text{ATP} + CO_2 + H_2O \qquad (3\text{-}9)$$

meaning not dependent on O_2. The third, the oxidative energy system, is referred to as the *aerobic* energy system. Energy transduction in this system is dependent on the presence of O_2. The discovery of direct linkages between glycolytic and oxidative processes and its impact on use of the terms *aerobic* and *anaerobic* will be discussed in Chapter 6.

■ Power and Capacity of Muscle Energy Systems

Although the maximal energy capacity of immediate (Table 3-2) and nonoxidative (Table 3-3) energy systems is small compared with that of the oxidative energy system (Table 3-4), immediate and nonoxidative energy systems are important because they are activated very rapidly when muscles start to contract. By comparison, the oxidative energy system is activated more slowly and produces energy at a lower rate even when fully activated. In Table 3-5 the maximal rates (power) at which the various systems provide energy for muscle contraction are contrasted with the maximal capacities (total contribution available) for energy release. In this comparison, immediate and nonoxidative energy systems are revealed to have superior, though smaller, power capacities. Thus, the three energy systems in muscle together provide a means to power short, intense bursts of activity as well as more sustained activities of lesser intensity.

TABLE 3-5

Maximal Power and Capacity of the Three Energy Systems

System	Maximal Power (kcal · min^{-1})	Maximal Capacity (Total kcal Available)
Immediate energy sources (ATP + CP)	36	11.1
Nonoxidative energy sources (anaerobic glycolysis)	16	15.0
Oxidative energy sources (from muscle glycogen only)	10	2000

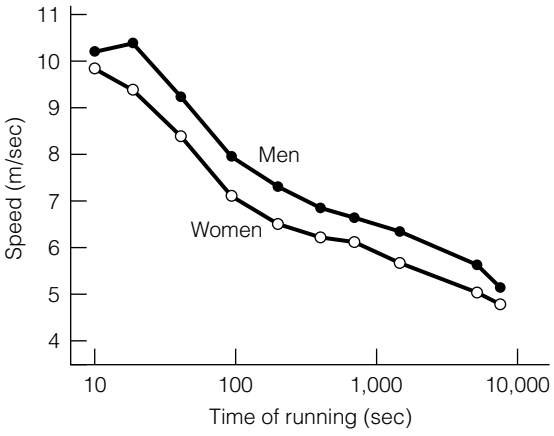

Figure 3-3 Plot of the average running speed maintained versus logarithm of time of event for men's and women's world running records. Note the presence of three curve components that suggest the presence of three energy systems. Data from the 1999 World list.

■ Energetics and Athletic Performance

Our interpretation that energy for the human engine comes from three sets of enzyme systems (Figure 3-2 and Table 3-5) is supported by an analysis of world running records (Figure 3-3). A plot of running speed versus time reveals three distinct curve components. Thus, it appears that the selection and training of athletes for athletic events requires knowledge of both the metabolic requirements of the activity and the metabolic characteristics of the individual. Because many athletic events and most of life's other activities take longer than 90 seconds, the primary importance of oxidative energy metabolism is obvious.

■ Enzymatic Regulation of Metabolism

The biochemical pathways that result in cellular energy transfer are discussed in the following chapters. Each of these pathways involves many steps,

each of which is catalyzed by a specific enzyme. It is important to note here, therefore, some functions of enzymes. Although enzymes cannot change the equilibria of reactions, they can lower the energies of activation, thereby allowing spontaneous reactions to proceed. Also, by linking exergonic to endergonic reactions through the use of ATP or other high-energy intermediates, enzymes facilitate endergonic processes.

The precise mechanisms by which enzymes operate are not completely understood, but some details of enzyme action are known. As illustrated in Figure 3-4a, enzymes are usually large molecules, in most cases with only a single site at which a reactant, or *substrate,* attaches. This site is called the *active site.* With a few exceptions, only the appropriate substrate interacts with an enzyme to induce a fit at the enzyme's active site. The combined substrate and enzyme are referred to as the *enzyme–substrate complex.* After the enzyme catalyzes the reaction, the products are released. Foreign substances that have the capability of competing for and occupying enzymatic sites are frequently poisons. An example is the hallucinogen LSD, which competes with the chemical messenger serotonin in the brain. "Bad" and recurring "free" trips occur because LSD binds in such a way that serotonin has difficulty displacing it.

Note also in Figure 3-4b that certain enzymes have binding sites other than the active site. When appropriate substances bind to these other sites, they affect the *configuration,* or *conformation,* of the active site. Therefore, the binding of these other factors affects the interaction of the enzyme with its substrate, thereby changing the rate at which the enzyme can function. Consequently, these factors that change catalytic rates of particular enzymes are termed *modulators.*

Modulators can be classified into two groups: Those that increase catalytic rates of enzymes are termed *stimulators,* and those that slow enzymatic function are called *inhibitors.* In the control of energy metabolism, ATP is the classic example of an inhibitor; ADP, AMP, and P_i are usually stimulators. In resting muscle, high levels of ATP inhibit carbohydrate, fat, and amino acid catabolism. However, when a muscle starts to twitch, ATP is degraded to ADP, AMP, and P_i. When these degradation products are formed, in the locus of their presence, they stimulate the mechanisms of ATP resupply.

The effect of various modulators on particular enzymes is called *allosterism,* referring to the fact that modulators change the spatial orientation, or shapes, of the parts of the enzymes. When several modulators are capable of affecting the catalytic rate of a particular enzyme, that enzyme is said to be *multivalent.* In coming chapters, we shall encounter several allosteric modulators. Among the most potent are those that phosphorylate (add phosphate, P_i) or dephosphorylate enzymes. An example of a multivalent allosteric enzyme is phosphofructokinase (PFK), a key enzyme of carbohydrate catabolism (Chapter 5). An example of an enzyme whose activity depends on phosphorylation is phosphorylase, a key enzyme in the degradation of glycogen (Chapter 6).

Different enzymes have different properties that have great effects on metabolism. Among these properties is the rate at which the enzyme functions. Maximum velocity (V_{max}) is an important descriptive parameter of enzymes. The Michaelis–Menten constant (K_M) describes the interaction of substrate and enzyme. The K_M is defined as the substrate concentration that gives half of V_{max}. V_{max} and K_M are illustrated in Figure 3-5. An appreciation for V_{max} and K_M is necessary because these parameters of a reaction tell us much about how fast that reaction will proceed and how the reaction rate is affected by changes in substrate concentration. In the following example, as well as in following chapters, we shall encounter many enzymes, substrates, and modifiers of enzyme function. In evaluating this material we will be well served to remember that at its essence, the rate at which any process proceeds depends on the kinetic properties (i.e., V_{max} and K_M) of the responsible enzymes.

The enzymes glucokinase and hexokinase have the same catalytic function: to phosphorylate and activate sugars for further metabolism (Chapter 5). These enzymes, however, have different catalytic activities, as measured by different V_{max} and K_M values. These different catalytic activities also allow

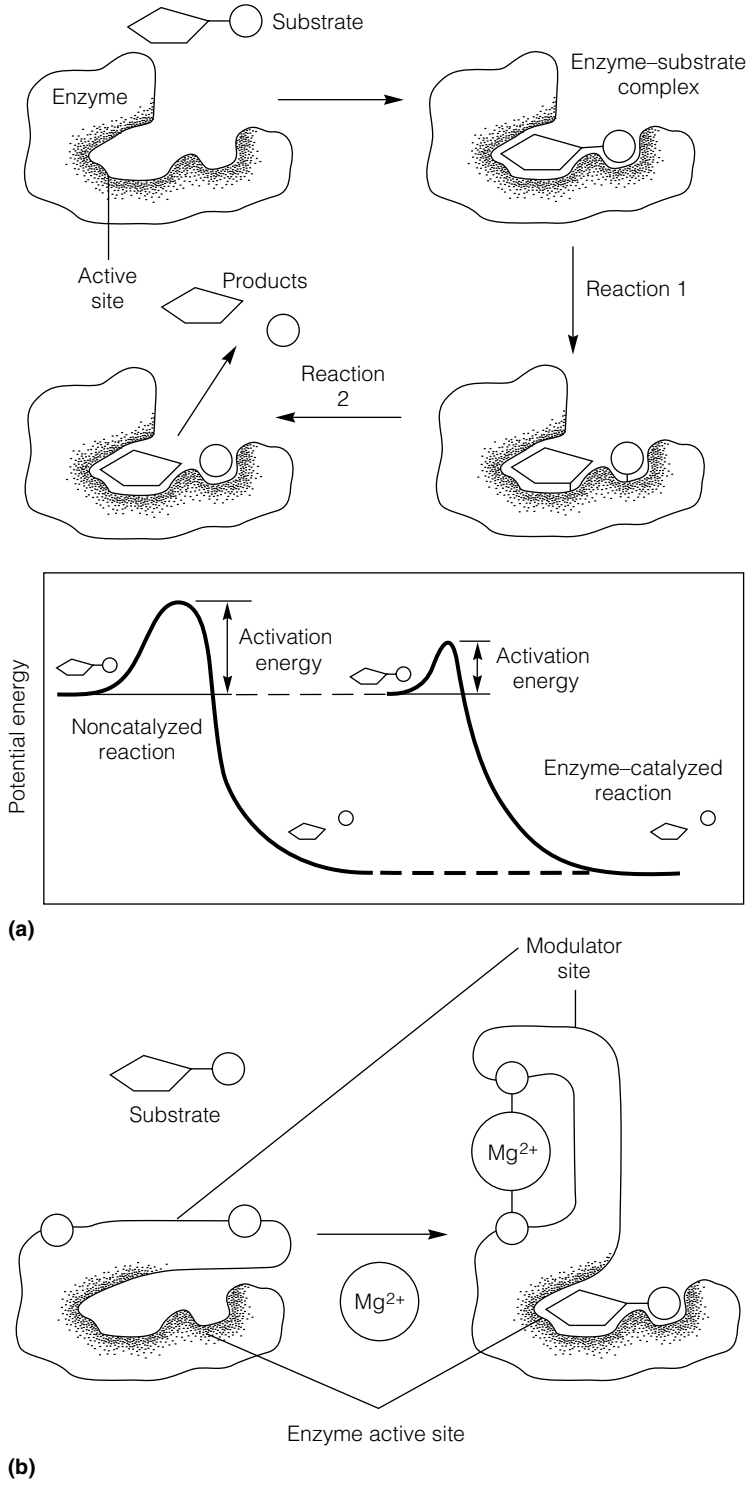

Figure 3-4 (a) Enzymes function, in part, by virtue of the substrate inducing a fit at the active site. By mechanisms still not completely understood, enzymes lower energies of activation, thereby increasing the probability of the reaction occurring. (b) Some enzymes have additional (modulatory) sites at which factors other than substrates bind. When binding occurs at these modulator sites, the three-dimensional shape of the enzyme is adjusted such that the probability of substrate binding at the active site is affected. Modulators can stimulate or inhibit catalytic function. Modified from A. J. Vander, J. H. Sherman, and D. S. Luciano, 1970. Used with permission.

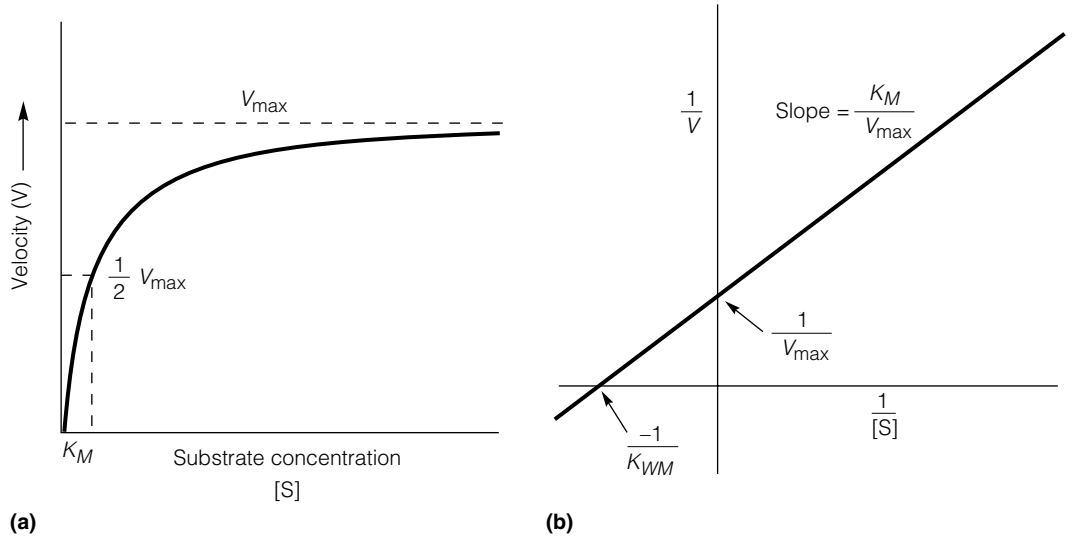

Figure 3-5 (a) Relationship between the maximum rate of catalysis for an enzyme and substrate concentration up to maximum (V_{max}) and its relation to the substrate (Michaelis–Menten constant, K_M). The K_M is the substrate concentration that gives 50% of V_{max}. Enzymes can vary in both V_{max} and K_M. (b) The Lineweaver–Burk double-reciprocal plot is a means for accurately predicting V_{max} and K_M, as well as for predicting the effect of inhibitors.

for different physiological functions. For example, at normal blood glucose concentration (5.5 mM), hexokinase in muscle would be maximally stimulated, whereas glucokinase in liver would not be very active (Figure 3-6). However, intracellular free glucose concentration is usually low (<1.0 mM) compared to the concentration in blood. Therefore, normally hexokinase (K_M = 0.1 mM) is very active, whereas glucokinase is relatively inactive. However, after eating, blood glucose in the portal vein perfusing the liver from the GI tract can exceed 10 mM, or more than twice arterial. Under this circumstance, free glucose concentration in liver cells rises to the point where hexokinase becomes activated to half or more of V_{max}. Thus, in this example, a "high K_M enzyme" such as glucokinase is sensitive to physiological changes in glucose concentration. In contrast, "low K_M enzymes" such as hexokinase probably operate at close to V_{max} *in vivo.*

■ Cell ATP Homeostasis and the Adenylate Energy Charge

Recall from Chapter 2 (Eq. 2-17) that the free energy of ATP (ΔG) in a cell is determined by the standard free energy ($\Delta G°'$) and by the ratio of products to reactants in solution. Therefore, the free energy of hydrolysis of ATP (ΔG_{ATP}) is

$$\Delta G_{ATP} = \Delta G°'_{ATP} + RT \ln [ADP]\,[P_i]/[ATP] \qquad (3\text{-}10)$$

where R is the gas constant and T the absolute temperature.

Analysis of this equation reveals several things related to cell energetics and its control. The ΔG_{ATP} (~ -11 kcal/mol) is usually more than the $\Delta G°'_{ATP}$ (-7.3 kcal/mol) for several reasons including that most of the adenine nucleotide is present in the form of ATP and concentrations of ADP and AMP (and P_i) are relatively small.

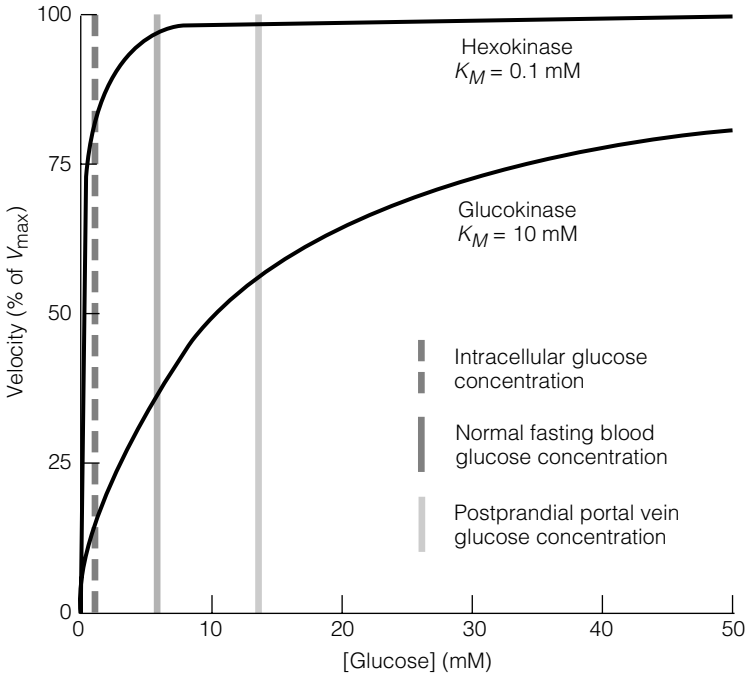

Figure 3-6 Illustration of the effects of K_M on physiological function. At levels of glucose in arterial blood and inside cells, hexokinase (a "low K_M enzyme") is fully activated. At the same concentrations, glucokinase (a "high K_M enzyme") is relatively inactive. Under postprandial (i.e., after eating) conditions, portal vein and hepatocyte glucose levels rise to where glucokinase becomes active. Thus, glucokinase is sensitive to changes in glucose availability, such as occurs after eating.

The realization that the ratio of ATP to associate metabolites is critically important in the regulation of cell metabolism is credited to Daniel E. Atkinson, who conceived of the *adenylate energy charge (AEC):*

$$\text{AEC} = 1/2\left(\frac{2[\text{ATP}] + [\text{ADP}]}{[\text{ATP}] + [\text{ADP}] + [\text{AMP}]}\right) \quad (3\text{-}11)$$

If all the adenine nucleotides are in the form of ATP, the AEC is 1.0. However, if all the adenine nucleotides are in the form of AMP, the ANEC is 0.0. *In vivo,* the AEC is regulated to be at 0.8, that is, with the adenylates mostly in the form of ATP. Thus, ATP-requiring reactions, such as ATP hydrolysis in muscle contraction, that perturb the AEC rapidly set into motion (activate) ATP-generating reactions such as glycolysis (Chapter 5) and oxidative phosphorylation (Chapter 6) to restore the AEC to its setpoint and, thus, preserve ATP homeostasis.

Despite intuitive first impressions, relative to the other constituents to the AEC, ATP is a poor controller. Cell systems are designed to maintain ATP homeostasis, so the level of ATP declines little during exercise. However, as shown by Lawrence Spriet and colleagues (Spriet et al., 2000), what changes in muscle during exercise are the levels of CP, ADP and AMP, and inorganic phosphate (P_i) (Figure 3-7). Because the AEC is a ratio, it declines if components in the numerator fall, and as well, the ratio declines if components in the denominator rise. Hence, the AEC tends to fall in muscle during contractions, because ATP is hydrolyzed and its degradation products rise in concentration even though the level of ATP is buffered from falling because of the actions of creatine kinase and creatine phosphate (CP).

Given the buffering of ATP level in working muscle by the CP, accumulations of ADP and AMP, particularly the latter, are powerful signals to activate processes to restore and defend ATP homeostasis.

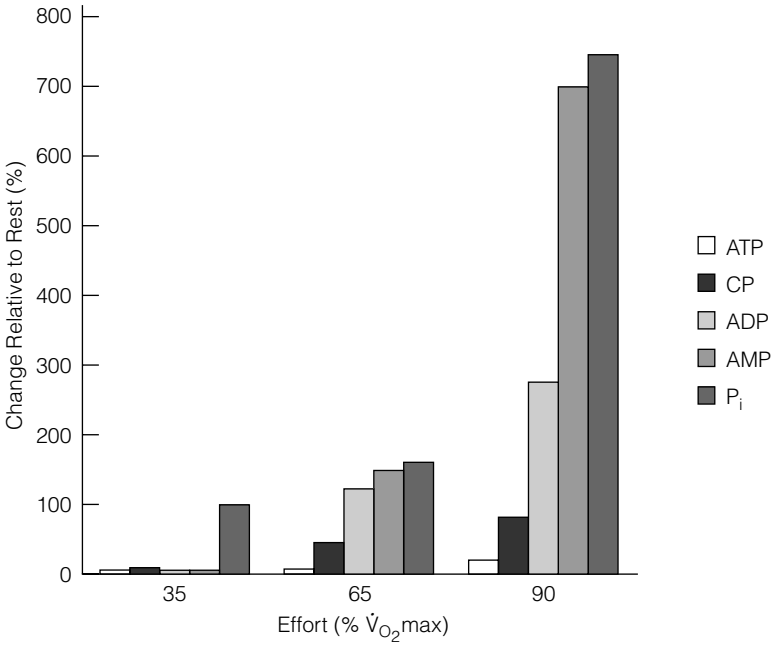

Figure 3-7 Relative changes in the concentrations of phosphagens and compounds related to ATP hydrolysis and maintenance of the cellular adenylate energy charge (AEC). Values determined in skeletal muscles of men during graded exercise. The concentration of ATP (i.e., the [ATP]) changes little relative to ADP, AMP, and P_i. Hence, ATP homeostasis is well-maintained in working muscle, but changes in ADP and AMP perturb the AEC, thus signaling counter-regulatory changes in glycolysis and oxidative phosphorylation to preserve [ATP]. The relative change in P_i is the greatest, but P_i is not included in computation of the AEC. P_i is, however, a powerful metabolic regulator that covalently modifies metabolic enzymes such as glycogen phosphorylase. Data modified from Spriet et al., 2000.

SUMMARY

One of the main principles in physiology and biochemistry is that of ATP homeostasis. Amazingly, the level of ATP can be maintained in working muscle because high ATP turnover rates yield byproducts, such as ADP, AMP, and P_i, that stimulate restoration of ATP to setpoint levels. Muscle cells with high capacities for ATP use are powerful, but fatigue rapidly if ATP level cannot be maintained. Cells with high capacities to restore ATP after use possess excellent endurance because ATP use and restoration are balanced and [ATP] maintained.

Processes of food and energy substrate catabolism in cells are usually linked to the process of ATP restitution. Approximately 50% of the potential chemical energy released from foodstuffs is captured in the common chemical intermediate, ATP. ATP, together with its storage form, creatine phosphate (CP), then serves as the immediate cellular energy source on which endergonic processes depend. ATP and CP not only supply immediate cellular energy sources, but their relative levels also stimulate or inhibit processes of energy metabolism. At rest, normally high levels of ATP and CP inhibit energy metabolism. When exercise starts, however, the utilization and decreased levels of ATP and CP, and the increased levels of ADP, AMP, and P_i, stimulate processes of energy metabolism. Enzymes interact with products of energy metabolism to regulate the rate at which specific processes proceed. Muscles utilize three different systems of energy release during exercise, each of which differs in mechanism, capacity, and endurance. Consequently, the rate and capacity for muscular power output is determined by the ability of these three systems that maintain cell ATP homeostasis.

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