

TABLE 9-1

Functions of ATP in Skeletal Muscle Contraction

1. Hydrolysis of ATP by myosin energizes the cross-bridges, providing the energy for force generation.
2. Binding of ATP to myosin dissociates cross-bridges bound to actin, allowing the bridges to repeat their cycle of activity.
3. Hydrolysis of ATP by the Ca^{2+} -ATPase in the sarcoplasmic reticulum provides the energy for the active transport of calcium ions into the reticulum, lowering cytosolic calcium to prerelease levels, ending the contraction, and allowing the muscle fiber to relax.

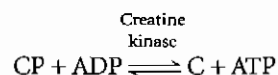
START READING HERE. SMALL BACKGROUND ON ENERGY USE IN MUSCLES FOLLOWED BY WHY MUSCLES FATIGUE.

Skeletal Muscle Energy Metabolism

As we have seen, ATP performs three functions directly related to muscle fiber contraction and relaxation (see Table 9–1). In no other cell type does the rate of ATP breakdown increase so much from one moment to the next as in a skeletal muscle fiber when it goes from rest to a state of contractile activity. The ATP breakdown may change 20- to several hundredfold depending on the type of muscle fiber. The small supply of preformed ATP that exists at the start of contractile activity would only support a few twitches. If a fiber is to sustain contractile activity, metabolism must produce molecules of ATP as rapidly as they break down during the contractile process.

There are three ways a muscle fiber can form ATP (Figure 9–22): (1) phosphorylation of ADP by **creatine phosphate**, (2) oxidative phosphorylation of ADP in the mitochondria, and (3) phosphorylation of ADP by the glycolytic pathway in the cytosol.

Phosphorylation of ADP by creatine phosphate (CP) provides a very rapid means of forming ATP at the onset of contractile activity. When the chemical bond between creatine (C) and phosphate is broken, the amount of energy released is about the same as that released when the terminal phosphate bond in ATP is broken. This energy, along with the phosphate group, can be transferred to ADP to form ATP in a reversible reaction catalyzed by creatine kinase:



Although creatine phosphate is a high-energy molecule, its energy cannot be released by myosin to drive cross-bridge activity. During periods of rest, muscle fibers build up a concentration of creatine phosphate approximately five times that of ATP. At the beginning of contraction, when the ATP concentration begins to fall and that of ADP to rise owing to the increased rate of ATP breakdown by myosin, mass action favors the formation of ATP from creatine phosphate. This energy transfer is so rapid that the concentration of ATP in a muscle fiber changes very little at the start of contraction, whereas the concentration of creatine phosphate falls rapidly.

Although the formation of ATP from creatine phosphate is very rapid, requiring only a single enzy-

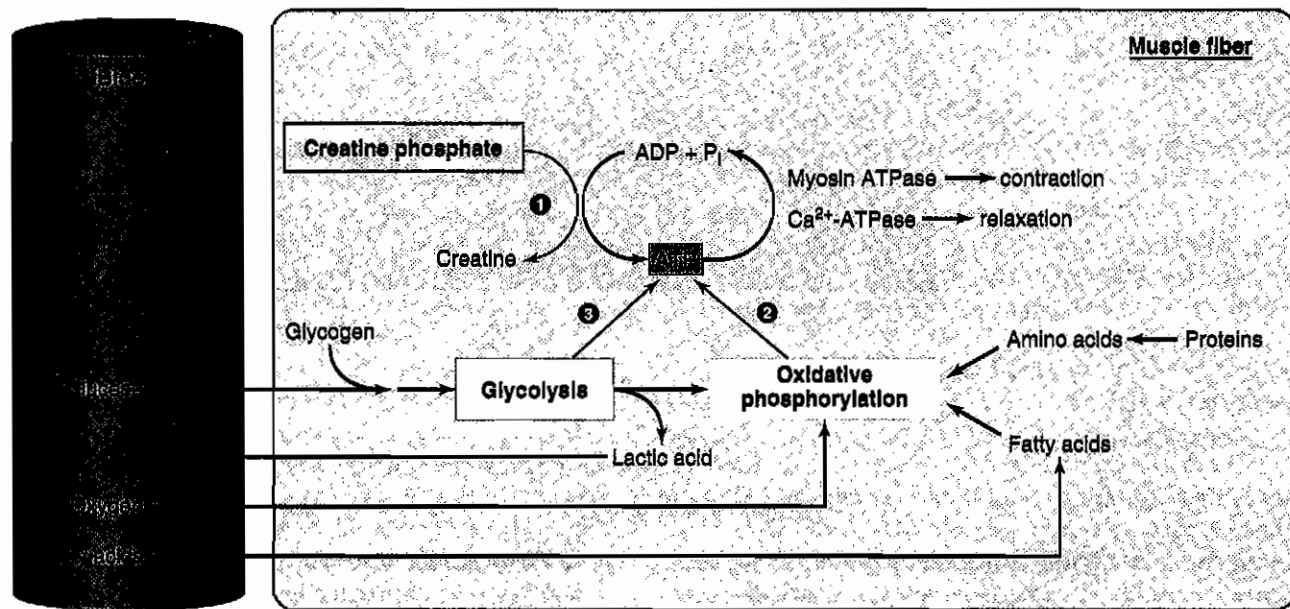


FIGURE 9-22

The three sources of ATP production during muscle contraction: (1) creatine phosphate, (2) oxidative phosphorylation, and (3) glycolysis.

matic reaction, the amount of ATP that this process can form is limited by the initial concentration of creatine phosphate in the cell. If contractile activity is to continue for more than a few seconds, the muscle must be able to form ATP from the other two sources listed previously. The use of creatine phosphate at the start of contractile activity provides the few seconds necessary for the slower, multienzyme pathways of oxidative phosphorylation and glycolysis to increase their rates of ATP formation to levels that match the rates of ATP breakdown.

At moderate levels of muscular activity, most of the ATP used for muscle contraction is formed by oxidative phosphorylation, and during the first 5 to 10 min of such exercise, breakdown of muscle glycogen to glucose provides the major fuel contributing to oxidative phosphorylation. For the next 30 min or so, blood-borne fuels become dominant, blood glucose and fatty acids contributing approximately equally; beyond this period, fatty acids become progressively more important, and the muscle's glucose utilization decreases.

If the intensity of exercise exceeds about 70 percent of the maximal rate of ATP breakdown, however, glycolysis contributes an increasingly significant fraction of the total ATP generated by the muscle. The glycolytic pathway, although producing only small quantities of ATP from each molecule of glucose metabolized, can produce large quantities of ATP when enough enzymes and substrate are available, and it can do so in the absence of oxygen (under anaerobic conditions). The

glucose for glycolysis can be obtained from two sources: the blood or the stores of glycogen within the contracting muscle fibers. As the intensity of muscle activity increases, a greater fraction of the total ATP production is formed by anaerobic glycolysis. This is associated with a corresponding increase in the production of lactic acid.

At the end of muscle activity, creatine phosphate and glycogen levels in the muscle have decreased. To return a muscle fiber to its original state, therefore, these energy-storing compounds must be replaced. Both processes require energy, and so a muscle continues to consume increased amounts of oxygen for some time after it has ceased to contract. In addition, extra oxygen is required to metabolize accumulated lactic acid and return the blood and interstitial fluid oxygen concentrations to pre-exercise values. These processes are evidenced by the fact that you continue to breathe deeply and rapidly for a period of time immediately following intense exercise. This elevated oxygen consumption following exercise repays the oxygen debt—that is, the increased production of ATP by oxidative phosphorylation following exercise is used to restore the energy reserves in the form of creatine phosphate and glycogen.

ONE EXPLANATION OF FATIGUE

Muscle Fatigue

When a skeletal muscle fiber is repeatedly stimulated, the tension the fiber develops eventually decreases even

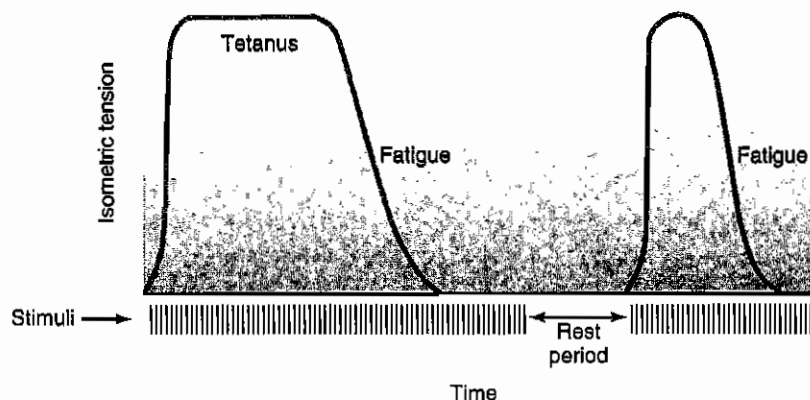


FIGURE 9-23

Muscle fatigue during a maintained isometric tetanus and recovery following a period of rest.

though the stimulation continues (Figure 9-23). This decline in muscle tension as a result of previous contractile activity is known as **muscle fatigue**. Additional characteristics of fatigued muscle are a decreased shortening velocity and a slower rate of relaxation. The onset of fatigue and its rate of development depend on the type of skeletal muscle fiber that is active, the intensity and duration of contractile activity, and the degree of an individual's fitness.

If a muscle is allowed to rest after the onset of fatigue, it can recover its ability to contract upon restimulation (Figure 9-23). The rate of recovery depends upon the duration and intensity of the previous activity. Some muscle fibers fatigue rapidly if continuously stimulated but also recover rapidly after a brief rest. This is the type of fatigue (high-frequency fatigue) that accompanies high-intensity, short-duration exercise, such as weight lifting. In contrast, low-frequency fatigue develops more slowly with low-intensity, long-duration exercise, such as long-distance running, which includes cyclical periods of contraction and relaxation. This type of fatigue requires much longer periods of rest, often up to 24 h, before the muscle achieves complete recovery.

It might seem logical that depletion of energy in the form of ATP would account for fatigue, but the ATP concentration in fatigued muscle is only slightly lower than in a resting muscle, and not low enough to impair cross-bridge cycling. If contractile activity were to continue without fatigue, the ATP concentration could decrease to the point that the cross-bridges would become linked in a rigor configuration, which is very damaging to muscle fibers. Thus, muscle fatigue may have evolved as a mechanism for preventing the onset of rigor.

Many factors can contribute to the fatigue of skeletal muscle. Fatigue from high-intensity, short-duration exercise is thought to involve at least three different mechanisms:

1. **Conduction Failure.** The muscle action potential can fail to be conducted into the fiber along the T-tubules, which halts the release of calcium from the sarcoplasmic reticulum. This conduction failure results from the buildup of potassium ions in the small volume of the T-tubule during the repolarization of repetitive action potentials. Elevated external potassium concentration leads to a persistent depolarization of the membrane potential, and eventually causes a failure to produce action potentials in the T-tubular membrane (due to inactivation of sodium channels). Recovery is rapid with rest as the accumulated potassium diffuses out of the tubule or is pumped back into the cell, restoring excitability.
2. **Lactic Acid Buildup.** Elevated hydrogen ion concentration alters protein conformation and activity. Thus, the acidification of muscle by lactic acid may alter a number of muscle proteins, including actin and myosin, as well as the proteins involved in calcium release. The function of the Ca^{2+} -ATPase pumps of the sarcoplasmic reticulum is also affected, which may in part explain the impaired relaxation of fatigued muscle. However, recent evidence has cast doubt on the role of lactic acid in fatigue, suggesting instead that this effect may be an artifact of experiments performed on muscle fibers at below-normal temperatures.
3. **Inhibition of Cross-Bridge Cycling.** The buildup of ADP and P_i within muscle fibers during intense activity may directly inhibit cross-bridge cycling (in particular step 2) by mass action. Slowing the rate of this step delays cross-bridge detachment from actin, and thus slows the overall rate of cross-bridge cycling. These changes contribute to the reduced shortening velocity and impaired relaxation observed in muscle fatigue resulting from high-intensity exercise.

**BUT WAIT, THERE IS MORE:
CNS FATIGUE**

With low-intensity, long-duration exercise, a number of processes have been implicated in fatigue, but no single process can completely account for it. The three factors just listed may play minor roles in this type of exercise as well, but it appears that depletion of fuel substrates may be more important. Although ATP depletion is not a cause of fatigue, the decrease in muscle glycogen, which supplies much of the fuel for contraction, correlates closely with fatigue onset. In addition, low blood glucose (hypoglycemia) and dehydration have been demonstrated to increase fatigue. Thus, a certain level of carbohydrate metabolism appears necessary to prevent fatigue during low-intensity exercise, but the mechanism of this requirement is unknown.

Another type of fatigue quite different from muscle fatigue occurs when the appropriate regions of the cerebral cortex fail to send excitatory signals to the motor neurons. This is called **central command fatigue**, and it may cause a person to stop exercising even though the muscles are not fatigued. An athlete's performance depends not only on the physical state of the appropriate muscles but also upon the "will to win"—that is, the ability to initiate central commands to muscles during a period of increasingly distressful sensations.

END READING