3.7 Muscle Energetics, Fatigue, and Training

Learning Objectives

- Explain why ATP is the "energy currency" of muscle cells
- List the major uses of ATP during contractions
- Explain the function of the creatine phosphokinase reaction in regenerating ATP
- Describe the myokinase reaction
- Describe the sources of glucose for muscle contraction
- Contrast the rate and capacity of ATP generation through glycolysis and oxidative phosphorylation
- Explain why lactic acid is produced by muscle
- Describe what is meant by the term "lactate shuttle" and describe the Cori cycle
- Explain why lactate release by muscle increases with vigorous exercise
- Describe the "anaerobic threshold" and its likely cause
- Describe the effect of exercise on glucose uptake by muscle
- Distinguish between fatigue at high intensity and low intensity exercises and explain the likely cause of fatigue in these two types of exercises
- Describe the ischemic exercise test and why it reveals defects in glycogenolysis
- Discuss the potential for transformation of muscle types in humans

MUSCULAR ACTIVITY RELIES ON THE FREE ENERGY OF ATP HYDROLYSIS

The cross-bridge cycle links shortening or force development to the hydrolysis of ATP. Through this cycle, chemical energy stored in the γ phosphate bond of ATP is made available for mechanical work. Thermodynamics tells us that the amount of work must be less than the chemical energy released. The chemical energy that is not converted to work is dissipated as heat. The free energy of ATP hydrolysis was given in Chapter 1.7 as

$$\Delta G = \Delta G^{0'} + RT \ln\left(\frac{[\text{ADP}][\text{Pi}]}{[\text{ATP}]}\right) \quad [3.7.1]$$

where $\Delta G^{0'}$ refers to the standard free energy change for ATP hydrolysis under the conditions of the cell—typically pH 7.0 and 37°C (310°K), and typical cell concentrations of Mg^{2+} and typical ionic strength. We have used -31.0 kJ mol^{-1} as this value, but the validity of this value for muscle tissue is uncertain. The values of [ATP], [ADP], and [Pi] are also uncertain because of methodological difficulties and the fact that the values can depend on which animal, which muscle, which muscle fiber, and the state of the muscle fiber. These concentrations may also vary with location within the muscle fiber. Some estimated values for human muscle at rest are: $[\text{ATP}] = 8.2 \times 10^{-3}$ M; $[\text{Pi}] = 3.8 \times 10^{-3}$ M; $[\text{ADP}] = 10 \times 10^{-6}$ M. Insertion of these values into Eqn [3.7.1] gives a calculated $\Delta G_{\text{ATP}\rightarrow\text{ADP+Pi}} = -62.7$ kJ mol^{-1}. During exercise, the concentrations of ATP, ADP, and Pi change and the free energy of ATP hydrolysis becomes less negative.

MUSCULAR ACTIVITY CONSUMES ATP AT HIGH RATES

In an intact muscle, macroscopic force is accompanied by thousands and thousands of cross-bridges cycling at rates that depend on the motor units that are recruited, the frequency with which they are recruited, and the type of muscle fiber (types I, IIA, or IIB). ATP hydrolysis is also used for Ca^{2+} reuptake into the SR and active ion pumping by the Na^+,K^+-ATPase to maintain the Na^+ and K^+ gradients necessary for the muscle action potential. Maintenance chores such as turnover of mRNA, lipids, and proteins also split ATP, but the actomyosin ATPase is the main sink for ATP during activity.

THE AGGREGATE RATE AND AMOUNT OF ATP CONSUMPTION VARIES WITH THE INTENSITY AND DURATION OF EXERCISE

The *rate* of ATP utilization by the aggregate muscles of the body depends on the intensity of the exercise. Intensity of exercise is determined by two variables: the recruitment of motor units and the frequency with which they are recruited. In weight lifting, for example, specific muscles are recruited for specific tasks such as the bench press. During a maximum lift, the primary muscle groups are recruited 100%, and they are recruited with tetanic stimulations. There is no rest phase for the muscles until the lift is completed. There is no more intense exercise than this for the specific muscles involved.

The *total amount* of ATP used during an exercise is its rate of utilization times the duration of the event. High

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intensity exercise can be maintained only for short periods, whereas moderate intensity exercise can be endured for long times. The relationship between intensity and sustainable effort is not linear. Maximal effort can be sustained for only a few seconds whereas high effort can often be sustained for much longer periods. Table 3.7.1 gives the approximate rate and amount of ATP needed for different track events. The amount needed for rest is not given because its duration is not specified.

IN REPETITIVE EXERCISE, INTENSITY INCREASES FREQUENCY AND REDUCES REST TIME

Figure 3.7.1 shows an electromyogram, or EMG, of leg muscles obtained from a slowly walking rat. The EMG is akin to an electrocardiogram (see Chapter 5.6): it is the trace of *electrical activity* of the muscle on the surface of the body. Larger EMG amplitudes (recorded in volts) indicate greater number of muscle fibers that are firing action potentials. Thus the EMG directly indicates activation and not force, but the expectation is that force would increase when the EMG amplitude increases. Each muscle is activated at appropriate times for definite lengths of time, and this activity is interspersed with periods of rest. In vigorous walking, the frequency of activation increases and the duration of each activation decreases. The **duty cycle**, the part of the time that the muscle is activated, typically increases with intensity because the period of activation decreases less than the period of rest. This describes the situation when we increase the speed of a repetitive action such as walking. In many animals, the speed of locomotion varies through a series of different sets of muscle coordination called gaits. In humans, walking and running form distinctive gaits, but running fast and running slow differ mainly in the speed and recruitment rather than the sequence of activation. Thus high intensity as applied to repetitive exercise means something different than in weight lifting: motor unit recruitment is increased, perhaps to 100%, but the muscles must be controlled by bursts of activation followed by rest periods. Intensity in this case is graded by recruitment and the duty cycle. In weight lifting, intensity is graded entirely by recruitment because the duty cycle is 1.0.

Each muscle fiber, when activated, is activated completely. The control of force for the aggregate muscle is achieved by the temporal recruitment of the fibers: which fibers are being activated and with what frequency and in what sequence, and not by control of the force of each motor unit or muscle fiber. Each activation entails fast rates of ATP hydrolysis as the actomyosin cross-bridges are activated by the Ca^{2+} transient.

TABLE 3.7.1 Rate and Amount of ATP Needed for Different Track Events

Event	Rate of ATP Consumption (mol/min)	Amount of ATP Needed (mol)
Rest	0.07	–
100 m sprint	2.6	0.4
800 m run	2.0	3.4
1500 m run	1.7	6
42,200 m marathon	1.0	150

Adapted from E. Hultman and H. Sjoholm, Biochemical causes of fatigue, in Human Muscle Power, *Human Kinetics Publishers, Inc., Champaign, IL, 1986.*

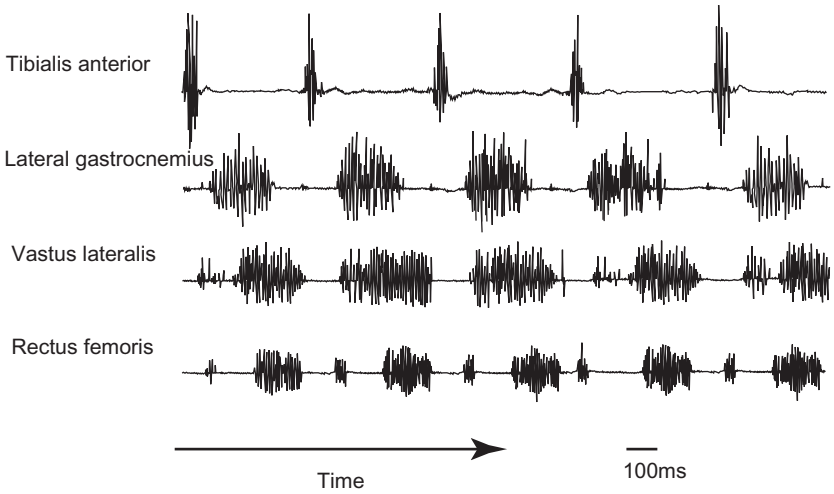

FIGURE 3.7.1 Electromyogram of leg muscles of rats walking slowly on a treadmill at a speed of 1 mph. The tibialis anterior muscle is in the anterior of the lower leg and lifts the foot. It is activated first. The gastrocnemius muscle is in the posterior lower leg, the calf, and extends the foot. The vastus lateralis and rectus femoris muscles are in the anterior thigh and extend the lower leg. *Modified from G.A. Brooks, T.D. Fahey, T.P. White, and K.M. Baldwin,* Exercise Physiology, *3rd ed, McGraw Hill, New York, NY, 1999.*

Increasing the frequency of activation necessarily decreases the time that the muscle is not activated, and this is the time the muscle has for metabolism to oxidize substrates produced during the contractions. Thus every muscle contraction requires rapid ATP consumption and rapid ATP regeneration, but at high intensity exercise there is less time for metabolism to recover the resting state. In the limit of maximum effort, there is no rest phase at all. This difference in maximum effort versus endurance exercise is the origin of the different kinds of fatigue generated by these different types of exercise.

METABOLIC PATHWAYS REGENERATE ATP ON DIFFERENT TIMESCALES AND WITH DIFFERENT CAPACITIES

Because active muscle uses ATP quickly, it must be regenerated quickly. Those systems that regenerate ATP quickly must themselves be regenerated in the rest phases. There are three major systems for the regeneration of ATP that differ in their capacity and rate:

1. Creatine phosphokinase and myokinase regenerate ATP fastest but with low capacity
2. Glycolysis regenerates ATP fast but with low capacity
3. Oxidative phosphorylation regenerates ATP slowest but with highest capacity.

These pathways are illustrated in Figure 3.7.2.

Muscles contain about 15−40 mM creatine phosphate. **Creatine phosphokinase** (CPK) catalyzes the phosphorylation of ADP from creatine phosphate to form ATP. This is an extremely rapid reaction that helps to "buffer" ATP concentrations near the normal 8 mM levels found in the myoplasm of muscle fibers. When creatine phosphate is used to regenerate ATP, myoplasmic [Pi] increases. It is believed that CPK is located very close to ATP-utilizing reactions such as the myosin ATPase and SR Ca-ATPase and may directly transfer ATP to these enzymes. This is called **substrate channeling**. These ATPase enzymes split ATP faster in the presence of CPK and creatine phosphate. **All contractions of muscle require creatine phosphate regeneration of ATP for maximum force**. Another enzyme, **myokinase**, converts two molecules of ADP into ATP and AMP. As ADP builds up in active muscle, AMP also builds up and may be a metabolic indicator of the fuel status of the cell.

Glycolysis breaks glucose into two pyruvate molecules and regenerates ATP from ADP and Pi. Regeneration of ATP requires the incorporation of Pi into 1,3-diphosphoglyceric acid from glyceraldehyde-3P, as shown in Figure 3.7.2. Glycolysis begins with glucose that may arise from muscle glycogen or from the blood. Glycolysis requires 2 ATP molecules and generates 4 ATP, for a net gain of only 2 ATP molecules per molecule of glucose. Additional ATP (3−5 per molecule of glucose) can be generated from the NADH produced by the oxidation of glyceraldehyde-3-phosphate. Glycolysis occurs in all muscle fibers, but the concentration of glycolytic enzymes differs. Fast-twitch glycolytic fibers depend most heavily on glycolysis for ATP regeneration.

The pyruvate formed in the cytoplasm by glycolysis enters the mitochondria to be converted to acetyl CoA by pyruvate dehydrogenase. In this process, 1 CO_2 is released. The acetyl CoA is converted to two more CO_2 molecules through the TCA cycle, which also produces NADH, $FADH_2$, and GTP. In the presence of oxygen, the NADH and $FADH_2$ are oxidized through the electron transport chain (ETC). The ETC pumps H^+ ions out of the matrix, establishing a $[H^+]$ gradient and an electrical potential across the inner mitochondrial membrane. This electrochemical gradient for H^+ is used by the mitochondrial F_0F_1ATPase, the **ATP synthase**, to synthesize ATP from ADP and Pi. Net ATP production from oxidative phosphorylation alone is about 25 ATP molecules per molecule of glucose. Oxygen is needed as the final electron acceptor from the ETC. Without oxygen, the ETC remains reduced and everything backs up. The TCA cycle stops for lack of NAD^+, and beta oxidation of fats stops for the same reason.

THE METABOLIC PATHWAYS USED BY MUSCLE VARIES WITH INTENSITY AND DURATION OF EXERCISE

Muscles can use fats, carbohydrates, and proteins as fuels. Which is used at what rates depends on the type, intensity, and duration of exercise. At rest, muscles use mainly free fatty acids (FFAs). At moderate exercise ($<$50% maximum O_2 consumption (V_{O_2})), muscles use blood glucose and free fatty acids. At higher intensities of exercise ($>$50% V_{O_2}), the proportion contributed by glycogen becomes increasingly important so that at 70−80% V_{O_2} aerobic metabolism of glycogen is predominant. During mild exercise of long duration, there is a gradual increase in dependence on FFA over glucose. Table 3.7.2 shows the rates of ATP production and amounts of ATP available from various sources. It is important to remember that every muscle contraction utilizes creatine phosphate and glycogen to lactate, but at low frequency the oxidation of lactate or blood glucose during the rest period provides energy to resynthesize creatine phosphate and glycogen.

AT HIGH INTENSITY OF EXERCISE, GLUCOSE AND GLYCOGEN ARE THE PREFERRED FUEL FOR MUSCLE

Muscle cells burn glucose, but the amount of free glucose is limited and cannot fuel muscle activity by itself. Muscles and liver store carbohydrates as glycogen. Sympathetic nervous activity and circulating epinephrine activate glycogenolysis, the breakdown of glycogen, to provide glucose for muscle activity. The enzyme phosphorylase in muscle and liver breaks down glycogen. It is activated by phosphorylation by phosphorylase kinase, which is in turn controlled by phosphorylation by protein kinase A, PKA. PKA is activated by 3′,5′cyclic AMP that is produced by adenylyl

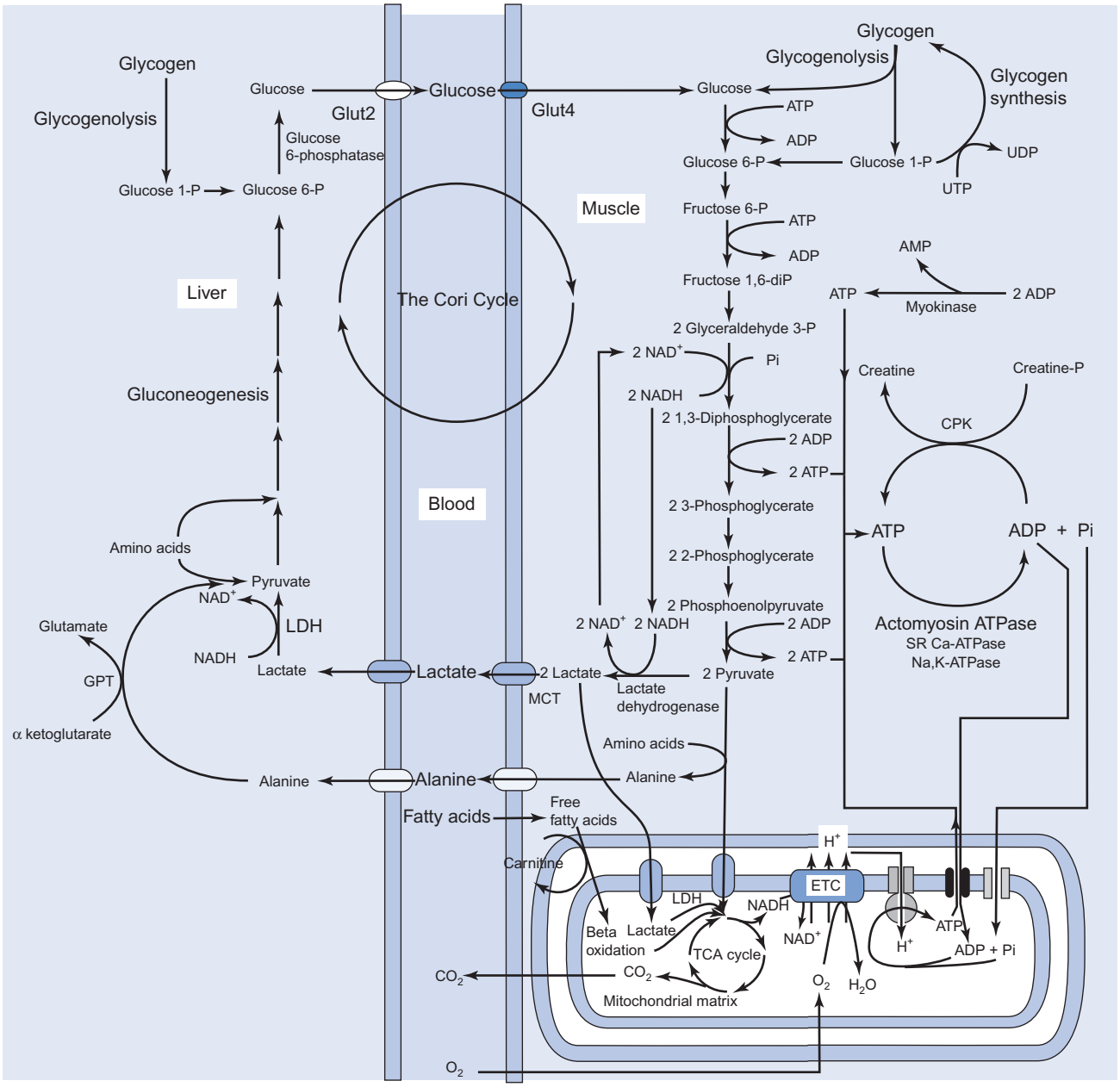

FIGURE 3.7.2 Overall energy metabolism driving contraction in skeletal muscle. ATP is consumed in a variety of reactions including the actomyosin cross-bridges and the SR Ca-ATPase pump. ATP is provided by a variety of routes including creatine phosphokinase (CPK) converting creatine P and ADP to ATP, glycolysis and complete oxidation of carbohydrates through the TCA cycle and electron transport chain (ETC). The source of glucose for glycolysis can be muscle glycogen or plasma glucose. The glucose is imported into the muscle by a glucose transporter, Glut4. Plasma glucose originates from liver and extrahepatic tissues either through glycolysis (liver) or gluconeogenesis (liver, kidneys, intestine). Fatty acids form acetyl CoA through beta oxidation and the acetyl CoA is then completely oxidized, in the presence of adequate oxygen, in the mitochondria. These fatty acids derive principally from adipose stores. When oxygen is insufficient to oxidize myoplasmic NADH, glycolysis continues by the regeneration of NAD^+ by converting pyruvate to lactic acid by lactate dehydrogenase (LDH). Production of lactic acid thereby allows glycolysis to continue. Lactic acid produced in this way is transported into the blood and from there to the liver where it can be converted to glucose again. This cycle of muscle glucose to lactate to liver lactate to glucose is the Cori cycle. Muscle also participates in the alanine–glucose cycle in which amino acids in muscle are converted to alanine and exported to the liver to make glucose by gluconeogenesis.

TABLE 3.7.2 Rate and Amount of ATP Available for Contraction from Various Fuel Sources

Source of Energy	Rate of ATP Production (mol/min)	Amount of ATP Available (mol)
ATP and creatine phosphate	4.4	0.7
Glycogen to lactate	2.4	1.6
Muscle glycogen to CO_2	1.0	84
Liver glycogen to CO_2	0.4	19
Fatty acids to CO_2	0.4	4000

cyclase following the activation of a G_s-coupled receptor. The rapid utilization of ATP in normal contractions appears to require glycogenolysis. Glycogen is partially regenerated during the resting phase of the muscle between trains of impulses.

Glycogen stored in muscle is dedicated to glycolysis because glycogenolysis produces G-1P and then G-6P, and muscle lacks **glucose-6-phosphatase** that converts G-6P to glucose. Glucose can cross the cell membrane over its transporter, but ionically charged G-6P cannot. Because muscle lacks the enzyme to make free glucose, muscle cannot export significant glucose. Liver and other tissues produce glucose that can travel to muscle through the blood. Muscle tissues take up glucose by a transporter, Glut4, that is sensitive to exercise. The Glut4 transporter is recruited to the cell membrane by insulin, but exercise also recruits Glut4 in the absence of insulin.

LACTIC ACID PRODUCED BY ANAEROBIC METABOLISM ALLOWS HIGH GLYCOLYTIC FLUX

As shown in Figure 3.7.2, glycolysis does not require oxygen to produce ATP, so this is called **anaerobic metabolism**, but it does reduce NAD^+ to NADH. The NAD^+ is an obligatory cofactor for the reaction of glyceraldehyde-3-phosphate to 1,3-diphosphoglycerate. If the cell runs out of cytoplasmic NAD^+, glycolysis will halt. Cytoplasmic NADH produced by glycolysis can be oxidized back to NAD^+ by the mitochondria through shuttle systems described in Chapter 2.10. Conversion of NADH to NAD^+ requires an oxidized electron transport chain. During rapid bursts of glycolysis, the mitochondria cannot keep up with the NADH generated and NAD^+ levels could fall. Lactic dehydrogenase converts pyruvic acid to lactic acid, simultaneously converting NADH to NAD^+. This NAD^+ can then be used to allow glycolysis to proceed at the glyceraldehyde-3-phosphate step. Thus **lactic acid production allows glycolysis to proceed during rapid glycolytic bursts of ATP production**.

MUSCLE FIBERS DIFFER IN THEIR METABOLIC PROPERTIES

Muscles can be classified by their mechanical properties (see Chapter 3.4) and by their myosin staining (see Chapter 3.5). Muscle fibers also differ in their metabolic capabilities. Peter and coworkers described three types of fibers: slow oxidative (SO), fast glycolytic (FG), and fast oxidative-glycolytic (FOG). Table 3.7.3 compares the various classification schemes.

The different muscle fiber types originate in the expression of different isoforms of muscle proteins and in the relative amount of different organelles in the cell. Red muscle fibers that contain a lot of myoglobin and mitochondria (giving them their red appearance) have a large oxidative capacity and they are slower and fatigue resistant. White muscle fibers containing little myoglobin and mitochondria are fast-twitch fibers that fatigue rapidly. Table 3.7.4 compares some of the different proteins expressed in different muscle types and the relative abundance of selected subcellular organelles.

Whole muscles contain thousands of muscle fibers that are distributed among the various muscle fiber types. Specific muscles may be predominantly composed of one muscle fiber type or another. The distribution of muscle fiber types within specific muscles varies with the individual.

The classification schemes shown in Table 3.7.3 are useful ways of organizing how we think about muscle, but they do not truly reflect the heterogeneity of muscle fibers. The muscle fibers are more continuous in the distribution of their characteristics, with gradations between them that are lost in the few classes that we recognize. Nevertheless, these schemes help us to think about how muscles do their job.

BLOOD LACTATE LEVELS RISE PROGRESSIVELY WITH INCREASES IN EXERCISE INTENSITY

Early studies of exercise showed a progressive rise in blood lactic acid with increasing intensity of exercise, as shown in Figure 3.7.3. Increased circulating lactic acid originates in the working muscles. Originally lactic acid was thought to be produced during anaerobic metabolism, so that the increased levels in the blood were thought to represent increased reliance on anaerobic metabolism. For this reason, the knee in the curve was called the "anaerobic threshold." The classical view is that lactate is produced only under anaerobic conditions, when muscle P_{O2} falls below levels that fully energize mitochondria. This view is now thought to be wrong. The main fact that does not fit is that lactate is produced by exercising muscles that are fully oxygenated. Lactic acid is normally part of muscle metabolism, but in high intensity exercise there is a mismatch between lactic acid production and oxidation.

TABLE 3.7.3 Muscle Fiber Type Classification Schemes

Classification Scheme	Muscle Property Used to Classify Types	Fiber Types
Burke	Mechanical properties	S, FR, FI, FF
Brooke	Myosin ATPase staining	I, IIA, IIB, IIC
Peter	Metabolic capacity	SO, FOG, FG

TABLE 3.7.4 Comparison of Selected Protein Isoforms and Organelles in Different Muscle Fiber Types

	Type I Muscle	Type IIa Muscle	Type IIb Muscle	Cardiac Muscle
Twitch	Slow	Fast	Fast	
Fatigue	Resistant	Resistant	Fatiguable	Resistant
Metabolism	Oxidative	Oxidative	Glycolytic	Oxidative
Mitochondria	+++	++++	+	++++
SR volume	++	+++	++++	+
Glycogen	+	+++	++++	++
Myosin heavy chain	MHC-I	MHC-IIa	MHC-IIb, -IIx	MHC-α, MHC-β
Myosin light chain	MLC-1aS, -1bS	MLC-1f, -3f	MLC-1f, -3f	MLC-1v, -1a
SR Ca-ATPase	SERCA2a	SERCA1a	SERCA1a	SERCA2a
Phospholamban	++	–	–	+
Calsequestrin	Fast and cardiac	Fast	Fast	Cardiac
RyR	RyR1	RyR1	RyR1	RyR2
Troponin C	TnC_1	TnC_2	TnC_2	TnC_1
Myoglobin	+++	+++	–	+++
Parvalbumin	–	+	++	–

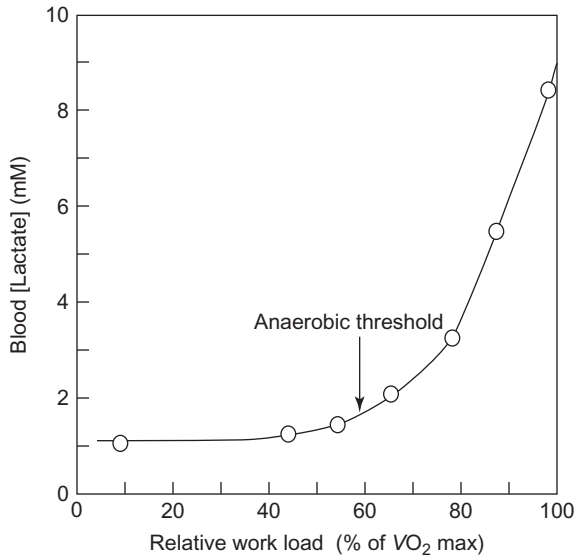

FIGURE 3.7.3 Blood lactate concentration as a function of relative work load. Lactate levels in blood increase only gradually until about 60% of $V_{O2\ max}$ is reached, and then lactate concentration increases markedly with further increases in exercise intensity.

MITOCHONDRIA IMPORT LACTIC ACID, THEN METABOLIZE IT; THIS FORMS A CARRIER SYSTEM FOR NADH OXIDATION

Mitochondria possess a monocarboxylic acid transporter (MCT1) that allows lactic acid to enter the mitochondria. Mitochondria also possess lactic dehydrogenase, LDH, which converts lactic acid to pyruvate. The pyruvate is then oxidized by the TCA cycle. The ability of lactic acid to enter the mitochondria and be converted back to pyruvate forms a pathway for the oxidation of cytoplasmic NADH, as shown in Figure 3.7.4. Lactic acid is not a shuttle system in that it is consumed by the mitochondria. Thus it is more like a carrier of reducing equivalents.

LACTATE SHUTTLES TO THE MITOCHONDRIA, OXIDATIVE FIBERS, OR LIVER

The fastest muscle fibers are expected to produce lactic acid at the highest rate. The first method of removing lactic acid is through mitochondria in the same cells that produce it. The lactic acid is taken up into the mitochondria by the MCT1 and the lactic acid is converted to pyruvate and oxidized. This intracellular shuttle is shown in Figure 3.7.5. When lactic acid production outstrips the capacity of lactic acid to be metabolized within the fast-twitch muscles, it spills out into the extracellular space. Some of this lactate is taken up by oxidative fibers, which are generally smaller than the large glycolytic fibers. Thus some of the lactic acid produced and released by muscle is metabolized in the muscle itself. This constitutes the cell–cell shuttle, also shown in Figure 3.7.5.

The liver can take up lactate that is released into the blood by the active muscles. The liver either metabolizes the lactate for energy or uses it to make new glucose through gluconeogenesis, and exports the glucose into the blood. Muscles can then take up this glucose and use it again for energy. This cycle of blood glucose to muscle lactate to blood lactate to liver lactate and back to blood glucose is called the Cori cycle, shown in Figure 3.7.5.

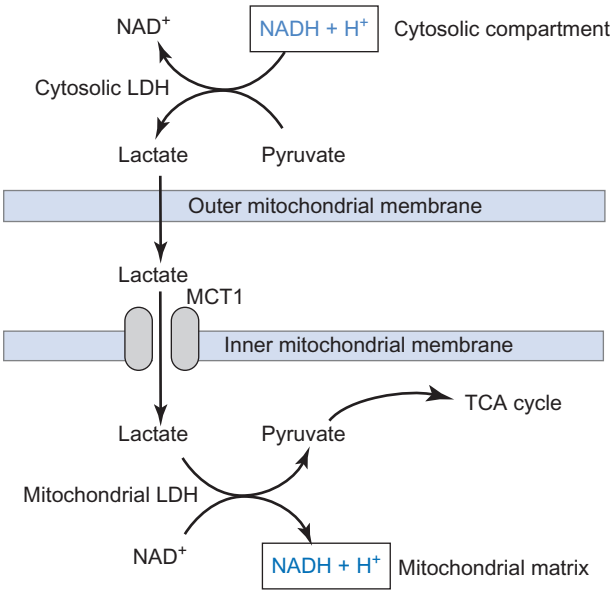

FIGURE 3.7.4 Lactic acid carries reducing equivalents into the mitochondria. Cytosolic NAD^+ is an obligatory requirement for glycolysis. Conversion of pyruvate to lactic acid in the cytoplasm regenerates NAD^+ so that glycolysis can continue. The lactic acid enters the mitochondria over the MCT1 carrier (which also transports pyruvate) and is converted back to pyruvate in the mitochondria by mitochondrial lactate dehydrogenase (LDH), which also converts NAD^+ to NADH in the matrix. The NADH generated in the mitochondria can be oxidized back to NAD^+ by the electron transport chain. The pyruvate can enter the TCA cycle through pyruvate dehydrogenase.

THE "ANAEROBIC THRESHOLD" RESULTS FROM A MISMATCH OF LACTIC ACID PRODUCTION AND OXIDATION

The increase in blood lactate with intensity of exercise results from the release of more lactic acid by the exercising muscles than can be metabolized by the aggregate tissues of the body. This has the appearance of an increase of anaerobic metabolism, and in one sense it is. Every muscle contraction involves "anaerobic" generation of ATP, meaning through the process of glycolysis. However, the tissue is not anaerobic. In less intense exercise, there is sufficient rest time for the lactic acid produced during this period to be oxidized. When exercise intensity increases, three different things happen:

1. The rest period between contractions becomes shorter.
2. The fast glycolytic fibers are increasingly recruited over the oxidative fibers, causing release of more lactic acid.
3. The sympathetic nervous system increases the rate of glycogenolysis, further increasing the supply of pyruvate, and, by mass action, the production of lactate.

Because of these events, lactate release by the active muscles soars with increased exercise intensity and outstrips the ability of the tissues to metabolize the lactate. This occurs without gross anaerobic conditions. The muscles are still fully oxygenated. There is no anaerobiosis, yet there is increased production of lactate by anaerobic pathways.

EXERCISE INCREASES GLUCOSE TRANSPORTERS IN THE MUSCLE SARCOLEMMA

Extracellular glucose enters muscle fibers through specific transporters, Glut4 transporters, in the muscle fiber membrane. The rate of uptake depends on the number of these transporters in the membrane and their activity. Insulin, an important hormone produced by the β cells in the islets of Langerhans in the pancreas, increases the uptake of glucose by the peripheral tissues, especially muscle, by recruiting Glut4 transporters from latent storage in vesicles in the muscle fiber. This mechanism is shown in Figure 3.7.6.

Contractile activity also increases the number of Glut4 transporters, but this effect is additive to the effect of insulin. Thus exercise itself exerts an insulin-like effect and increases glucose uptake without increases in insulin. The mechanism by which exercise increases Glut4 transporters is not yet completely worked out. However, researchers believe that AMPK, a protein kinase stimulated by AMP, and calmodulin-dependent protein kinase, CAMK, may be involved. AMPK is stimulated by AMP, which is produced from ADP by myokinase when ADP concentrations rise during contractions. The AMPK is thought to be a kind of "fuel gauge" that senses low fuel levels and then switches off ATP-consuming reactions and turns on ATP-producing reactions. AMP acts in a negative feedback mechanism to restore ATP levels. AMPK phosphorylates AS160 (Akt substrate molecular weight 160 kDa), a GTPase-activating protein (GAP) that inactivates Rab. The human genome codes for over 60 Rabs, which are involved in vesicular tethering to the cytoskeleton, trafficking and docking and fusion to membranes. Rab is active when it is bound to GTP. Its GTPase activity splits GTP to GDP, and then Rab is inactive. AS160 activates the GTPase of Rab, thereby inactivating Rab. Phosphorylation of AS160 converts it to an inactive state, which thereby activates Rab by removing AS160 inactivation. How contraction causes Glut4 insertion into the plasma membrane is presently unknown, but it probably involves CAMK, NO, and AMPK. CAMK is activated by Ca^{2+} when it rises to activate the myofilaments. If it simultaneously activates Glut4 transporters, it acts as a feed-forward mechanism to begin increasing ATP supply in anticipation of its need to support contraction. PKC, CAMK and nitric oxide, NO, are all increased after activity and are thought to result in increased Glut4 incorporation into the surface membrane, but the mechanisms by which this happens are not yet worked out.

Because exercise has an insulin-like effect on glucose uptake by muscles, diabetic persons who inject insulin must cut back on their insulin shots when they anticipate they will exercise.

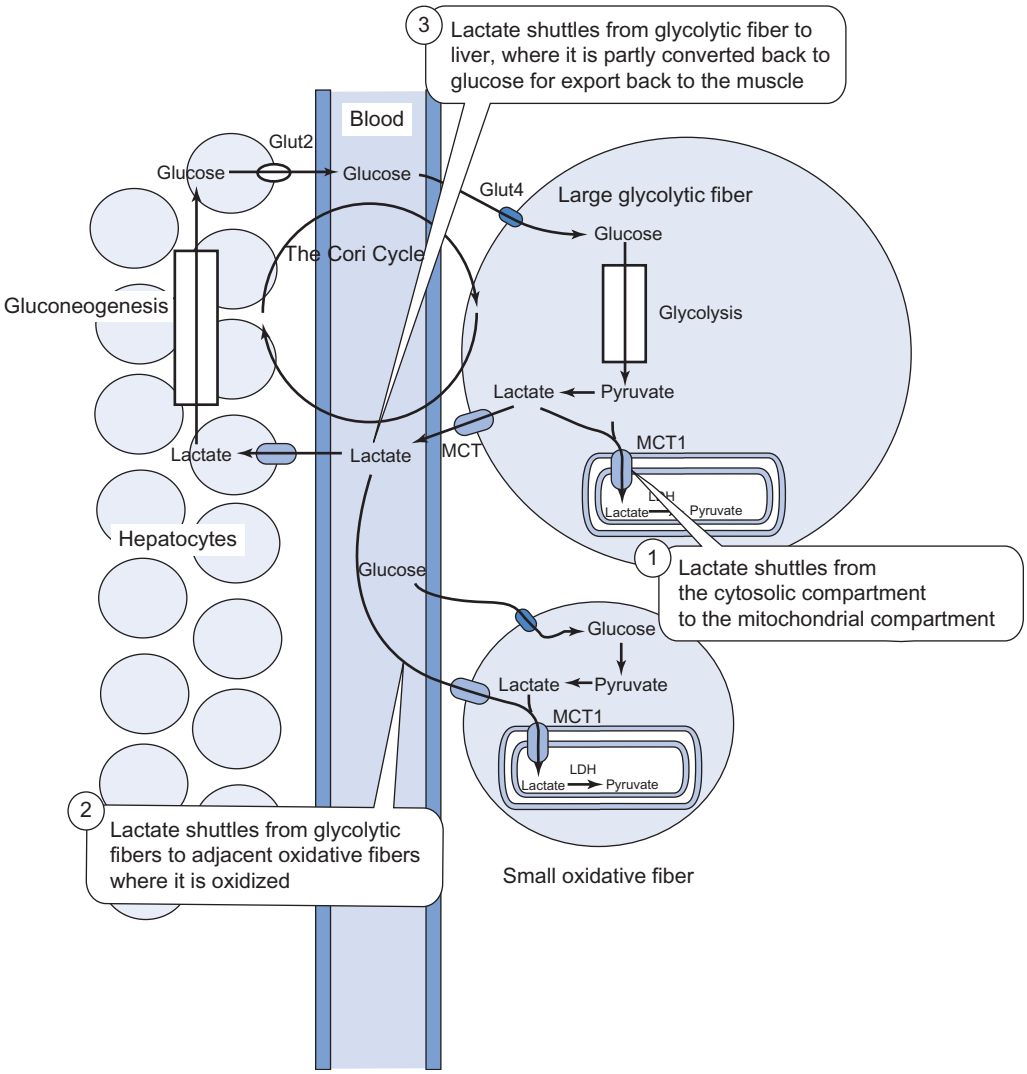

FIGURE 3.7.5 The lactate shuttles. Lactate is produced in the cytoplasm by LDH acting on pyruvate and NADH. Lactate can be shuttled from the cytoplasmic compartment to the mitochondrial compartment by importing the lactate into the mitochondria and linking it to the synthesis of pyruvate and the generation of NADH in the mitochondrial matrix. This is the intracellular lactate shuttle. Secondly, lactate can be exported into the blood where it is taken up by adjacent oxidative muscle fibers and completely oxidized by their mitochondria. This is the cell-to-cell lactate shuttle. Third, lactate released into the blood when lactic acid production is high can be taken up by liver cells (also called hepatocytes). The hepatocytes resynthesize glucose from the lactate and export it back into the blood where it can be taken up by the exercising muscle, for example. This is the Cori cycle.

FATIGUE IS A TRANSIENT LOSS OF WORK CAPACITY RESULTING FROM PRECEDING WORK

There are two types of fatigue. Exercise performed at submaximal effort for many repetitions eventually results in a loss of the ability to generate the submaximal force. This fatigue takes some time to develop and time to recover from. The second type of fatigue occurs at maximal effort. This involves maximal recruitment and a sustained volley of nerve impulses to continuously activate the muscle with no rest phase. Fatigue here is rapid in onset and also recovers rapidly. The definition of a maximum bench press is that you cannot do it twice, so fatigue in this sense occurs within seconds.

Because submaximal effort can be anything from near maximum to very light, fatigue can occur in a continuous spectrum of effort and repetitions. These two archetypes of many repetitions and light load versus a single effort at maximal load have different mechanisms for the origin of the fatigue.

FATIGUE HAS MULTIPLE CAUSES

Anything that happens from the cerebral cortex where motor commands originate, to the lower motor neuron where the signals are integrated, to the neuromuscular junction, EC coupling, and formation of cross-bridges are potential sites for partial failure during fatigue. We might expect that the cause of fatigue will not be the same along the spectrum of effort and repetition.

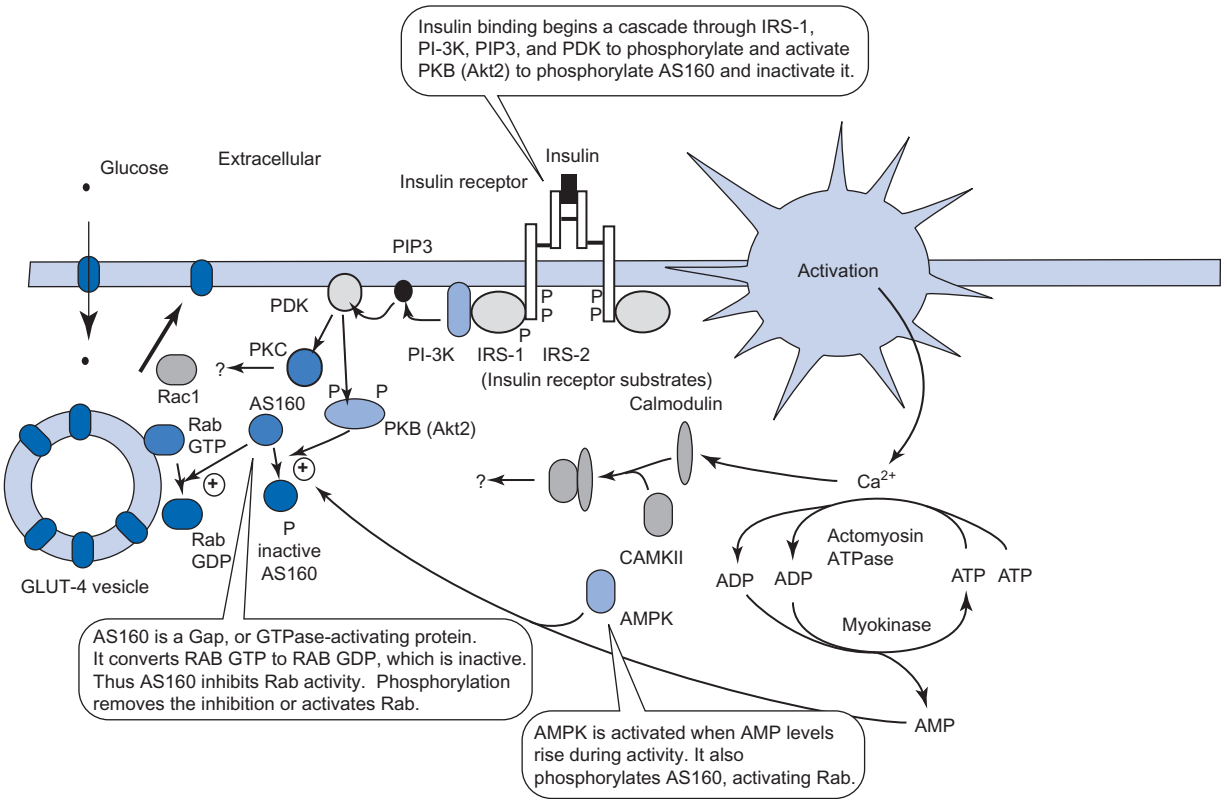

FIGURE 3.7.6 Insulin and exercise increase GLUT4 incorporation into the sarcolemma of muscle fibers by recruiting transporters from a population of latent transporters located in vesicles in the cell. The increased numbers of GLUT4 transporters increase glucose uptake and generation of ATP through glycolysis and oxidation of pyruvate or lactate. Insulin binds to its receptor, a receptor tyrosine kinase, that phosphorylates IRS-1, insulin receptor substrate 1, and transphosphorylates itself. IRS-1 activates PI-3K, phosphatidylinositol 3-kinase, that increases the concentration of PI 3,4,5-P_3 that, in turn, activates PDK, phosphatidylinositol-dependent kinase. PDK phosphorylates PKB (protein kinase B, also called Akt—in this case Akt2). Active PKB phosphorylates AS160, Akt substrate with molecular weight 160 kDa. AS160 in its unphosphorylated state is a GAP, GTPase-activating protein, that stimulates the GTPase activity of Rab proteins on GLUT4 vesicles within the cell. Active Rab is part of the machinery involved in trafficking of the vesicles towards the cell membrane and fusion of the membrane with the sarcolemma. Active Rab has GTP bound. Thus, AS160, by stimulating Rab GTPase activity, converts it from the active to inactive state. Phosphorylation of AS160 makes AS160 inactive and thus preserves active Rab-GTP. In this way, insulin stimulates the incorporation of GLUT4 into the membrane. Activity of the muscle also does this, but through separate paths that converge onto Rab. During activity, AMP levels rise and activate AMPK (AMP Kinase) that also phosphorylates AS160. Calmodulin-dependent protein kinase (CAMK) is also thought to increase GLUT4 incorporation, but its targets are not yet certain.

IN HIGH INTENSITY, SHORT DURATION EXERCISE, FATIGUE IS LIKELY DUE TO INCREASED CYTOSOLIC PI

In high intensity, very short duration exercise such as maximum weight lifting, it is thought that fatigue resides in the muscles alone. Here athletes have extremely strong motivation and most likely recruit all of their muscle fibers. Since the last recruited fibers are generally fast-twitch fibers that fatigue easily, reduction in force with continued effort is likely due to reduced force in those fibers. In fast-twitch fibers activated for short bursts, creatine phosphate regenerates ATP from ADP. The terminal phosphate comes from the creatine phosphate, so that the regeneration of ATP from creatine phosphate results in a large buildup of Pi in the myoplasm. At the same time, the activation of anaerobic glycolysis results in ATP production with a buildup of lactic acid and H^+ ions (due to dissociation of the acidic group on lactate). During exercise, the pH of muscle can fall from pH 7.0 to pH 6.0. Formally it was believed that H^+ interferes with force production, either by directly inhibiting the actomyosin ATPase or by making the myofilaments less sensitive to activator Ca^{2+}. This effect is now thought to be less important, whereas Pi can inhibit force development both by interfering with cross-bridge cycling and by reducing the Ca^{2+} transient. Because creatine phosphate content in fast-twitch fibers can reach as high as 40 mM, regeneration of ATP can increase [Pi] higher than 20 mM. At these concentrations, Pi can enter the SR and precipitate Ca^{2+} within the lumen, making it less available for release during E–C coupling. The resulting reduction in force is perceived as fatigue. **High intensity, short duration exercise causes fatigue mainly through increased cytoplasmic [Pi].**

IN LONG DURATION, REPETITIVE EXERCISE, FATIGUE IS SHARED WITH GLYCOGEN DEPLETION AND CENTRAL FATIGUE

Central fatigue is the term given to the reduction in force related to reduced recruitment by the central nervous system. Peripheral fatigue involves any changes within the muscle that leads to a reduced response to neural

excitation. We all have the subjective experience of being fatigued, and that accomplishing a motor task requires an extra dose of mental effort when we are fatigued. How do we obtain the subjective perception of fatigue?

Evidence is mounting that group III (thinly myelinated fibers) and group IV (unmyelinated fibers) carry afferent information from muscle fibers to the dorsal horn of the spinal cord and from there affect both spinal and supraspinal sites. The output of group III and IV fibers increases during exercise and stays increased for the duration of the exercise. Input from these fibers increases blood flow to active muscles and increases ventilatory drive during exercise. This assures oxygen and nutrient supply to the exercising tissues and helps prevent peripheral fatigue in exercising muscles. The output of group III and IV fibers appears to inhibit spinal motor neurons and, presumably, it is the group III and IV supraspinal effects that give rise to the subjective perception of fatigue. It appears that there may be more than one type of receptor involved in these afferent signals. One type, the so-called metaboreceptors or ergoreceptors, respond to normal levels of ATP, lactate, and $[H^+]$ associated with nonfatiguing exercise. A second type, metabonociceptors, respond to higher concentrations of these materials that is associated with fatigue or damage to the tissues.

The performance times at high but submaximal workloads depend on the size of the glycogen stores before exercise. Fatigue appears when glycogen levels fall but before they are zero. This has led to the hypothesis of the "glycogen shuttle" in which glycogenolysis is necessary to maintain ATP during contraction, and it is resynthesized during the rest period between contractions. When glycogen becomes low, it can no longer sustain ATP levels during contraction and force falls, even though glycogen is not completely used up. Thus **low intensity, long duration exercise causes fatigue through glycogen depletion**. This explanation has led to the training regimen of **carbohydrate loading** to postpone fatigue during endurance athletic events. In this regimen, glycogen stores are increased by a combination of exercise and carbohydrate consumption. It is usually accomplished by exhaustive exercise followed within 2 h by a high-carbohydrate meal. Under these conditions, the glycogen stores **supercompensate** and stores larger than normal amounts of glycogen.

GLYCOGENOSES SHOW THE IMPORTANCE OF GLYCOGEN TO EXERCISE

Persons with deficits in the enzymes involved in glycogen metabolism have exercise intolerance (see Clinical Applications: Muscle glycogenoses and Figure 3.7.7). However, the mechanism by which glycogen depletion impairs force development remains unknown. If the only function of glycogen is to regenerate ATP, then the proximate cause of muscle force decline should be reduced ATP concentrations or increased ADP and Pi. But fatigue in endurance exercise appears to be unexplained by gross reductions in ATP or increases in ADP and Pi. The key appears to be in the heterogeneity of glycogen stores. Glycogen is located in three separate compartments in the muscle fiber: (1) subsarcolemmal glycogen; (2) intermyofibrillar glycogen (between the myofibrils); and (3) intramyofibrillar glycogen (within the myofibrils). Glycogen in these compartments is used to fuel specific activities of the cell. The subsarcolemma glycogen fuels the surface membrane Na,K-ATPase, whereas the intramyofibrillar glycogen fuels the SR Ca-ATPase. The intramyofibrillar pool of glycogen is depleted more readily by exercise. The hypothesis is that glycogen depletion in this compartment reduces Ca^{2+} release by the SR, so that the contraction in response to excitation has reduced force, i.e., the muscle fiber is fatigued.

INITIAL TRAINING GAINS ARE NEURAL

During initial training (the first few weeks) of naïve subjects, the maximal voluntary contraction increases whereas the maximal evoked contraction (produced by direct and maximal stimulation of the motor nerve) does not. This suggests that trainees learn to activate their muscles more fully or they improve coordination of the voluntary contraction. Increases in maximal evoked contraction require longer training. Thus early and rapid strength gains come from training the brain.

MUSCLE STRENGTH DEPENDS ON MUSCLE SIZE

The maximum force that can be exerted by a muscle depends on its cross-sectional area and architecture such as pinnation. Strength training employs contractions against large resistances with few repetitions. It is called **resistance training**. Beginning training is associated with **delayed onset muscle soreness** or **DOMS**. Part of the soreness could be due to stretching of sensory neurons either from edema or from mechanical stretch. The afferent information is probably carried by unmyelinated fibers from the muscle. The exercise signals muscle hypertrophy: the diameter of the fibers increases but the number of fibers stays the same. It may be that some limited amount of hyperplasia (increase in cell number) may also occur. Both type I and type II fibers increase in size in response to heavy resistance training. Hypertrophy occurs two ways: muscle fibers make more myofibrils and satellite cells within the muscle fuse with existing muscle fibers to help control the additional cytoplasm. During development, satellite cells are recruited to form myotubes that further differentiate to become muscle fibers. The signals for muscle hypertrophy are summarized in Figure 3.7.8.

ENDURANCE TRAINING USES REPETITIVE MOVEMENTS TO TUNE MUSCLE METABOLISM

Endurance training increases the capillarity of muscles and tunes the muscles' metabolic capabilities. Concentrations of myoglobin and TCA cycle enzymes are increased as well as both the size and number of mitochondria. Muscles of endurance-trained subjects use fats

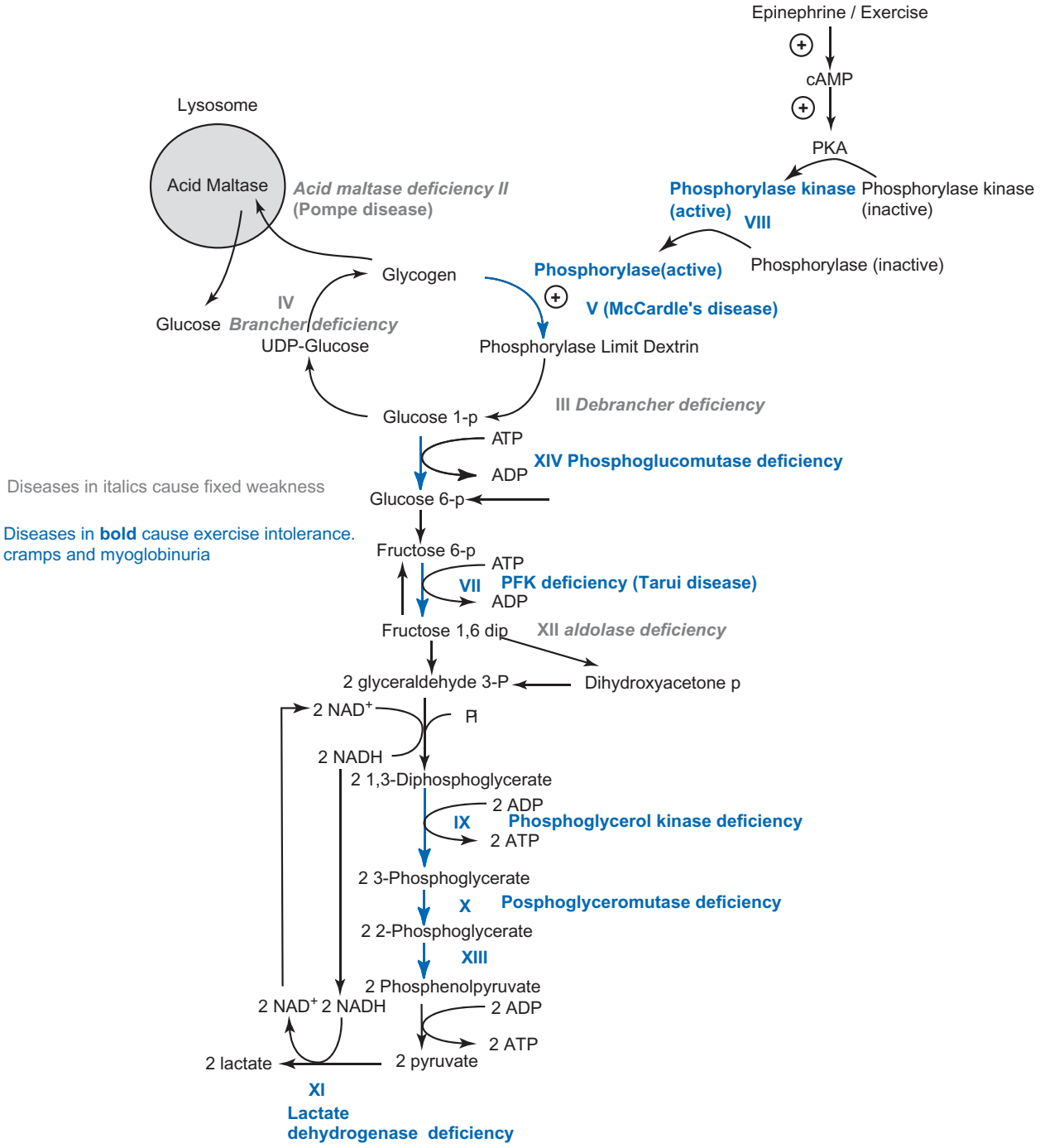

FIGURE 3.7.7 Muscle glycogenoses. Muscle glycogenoses are a group of inherited diseases of glycogen storage or utilization. They present with either exercise intolerance, fatigue, cramps and myoglobinuria, or fixed muscle weakness. Those shown in italics present with fixed muscle weakness. Those shown in the figure in bold present with exercise intolerance, cramps, fatigue, and myoglobinuria. Myoglobinuria typically does not show up unless exercise is strenuous. Many persons afflicted with these diseases learn to exercise within their limits and so maintain fairly normal life styles.

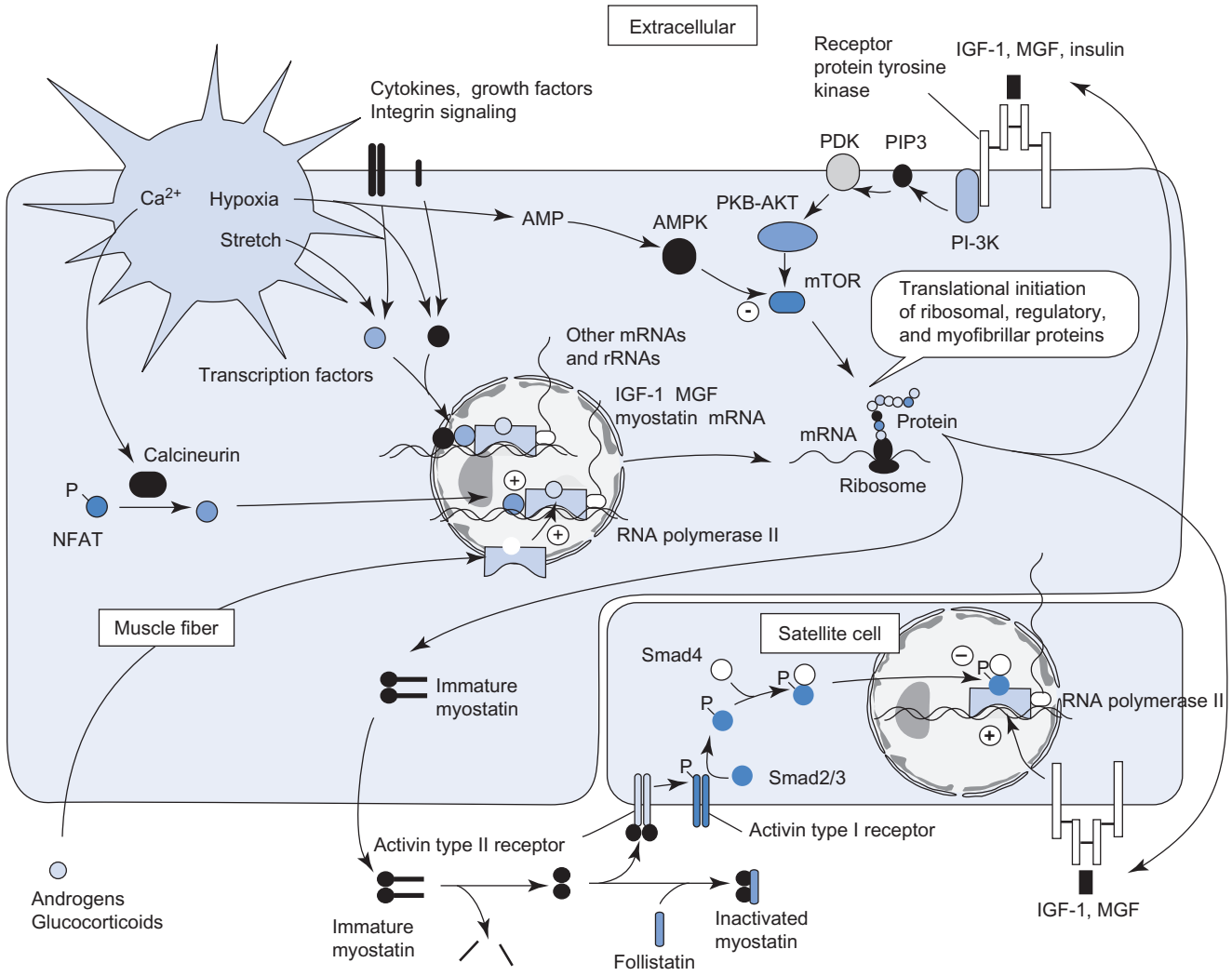

FIGURE 3.7.8 The signaling events in muscle hypertrophy. Muscle grows in response to stretch, increases in the integrated cytoplasmic [Ca^{2+}], androgens, glucocorticoids, and cytokines. Calcium activates calcineurin, a protein phosphatase that dephosphorylates NFAT (nuclear factor of activated T cells) and activates it. Myostatin produced by muscle inhibits satellite cell division and differentiation. Muscle cells also respond to IGF-1 (insulin-like growth factor-1) and MGF (muscle growth factor). Myostatin is also known as growth and differentiation factor 8 (GDF-8). It is a member of the transforming growth factor β family (TGFβ). It is secreted as an inactive peptide that dimerizes and is then cleaved to its active form. Follistatin, another regulator, can bind to myostatin and inhibit it. Myostatin binds to activin receptor type IIB. This phosphorylates activin receptor type I. (These activin receptors are serine–threonine protein kinases; there are currently 5 type II and 7 type I receptors. The type I receptors are also referred to as activin-like kinases, or ALK1, ALK2, and so on.) The activated activin receptor type I then phosphorylates members of a family of proteins called Smads. Eight different Smads have been identified in mammals. These Smads then control gene expression in the muscle fiber and satellite cells.

as the primary fuel for moderate exercise, thereby sparing glycogen for bursts of high intensity activity.

ENDOCRINE AND AUTOCRINE SIGNALS REGULATE MUSCLE SIZE (=STRENGTH)

Growth hormone is secreted by the anterior pituitary. It induces the liver to form insulin-like growth factor (IGF-I) that circulates in the blood. Muscles have receptors for IGF-1 that activate the cascade leading from phosphatidylinositol 3-kinase (PI-3K) to activation of protein kinase B (PKB-AKT) and mammalian target of rapamycin (mTOR) that stimulate muscle growth. This is inhibited by AMP-dependent protein kinase when AMP levels rise during hypoxia, for example. Muscles are also responsive to anabolic steroids and androgens. This is the basis for the generally greater strength and muscle size in men compared to women.

Myostatin is an autocrine and paracrine hormone produced by muscle cells that inhibits muscle differentiation and growth. Knockout mice without myostatin and certain breeds of cattle (Belgian Blue and Piedmontese) that lack effective myostatin are "double muscled." Because myostatin also targets adipocytes, these animals also lack adipogenesis (formation of fat) and so they are lean as well. A report was published about a young boy who had a myostatin mutation that is associated with gross muscle hypertrophy (*New England Journal of*

Clinical Application: Muscle Glycogenoses

Muscle glycogenoses are a group of inherited defects in enzymes that deal with glycogen storage or utilization, or carbohydrate metabolism. Their clinical presentations take two forms. One form presents with exercise intolerance, with cramps, fatigue, and myoglobinuria that results from breakdown of the muscle fibers and spilling of myoglobin into the blood (**rhabdomyolysis**) and from there into the urine. The second form presents with a progressive muscle weakness. There are number of different types of glycogenoses, and some of these are shown in Figure 3.7.7. They differ in the enzymes affected, but many of these defects have subtypes that differ in their specifics. The iconic example of glycogenoses is **McArdle's disease**, a deficiency of muscle phosphorylase. McArdle's disease is also known as glycogen storage disease V (GSD V). Without muscle phosphorylase, muscle glycogen cannot be broken down to glucose-1-phosphate and so muscles cannot use the glycogen for ATP production. The result is an exercise intolerance. In persons with a deficiency of debrancher enzyme, GSDIII, glycogen can be broken down to limit dextrins, and some glucose-1-phosphate can be produced. The result is muscle weakness rather than exercise intolerance.

Glycogenoses can be diagnosed through genome sequencing, but they can also be diagnosed clinically through the ischemic exercise test. In this test, an iv cannula with a three-way valve is inserted into a large vein in the forearm. A blood sample is obtained 2 minutes before exercise as a baseline. A pressure cuff around the upper arm is inflated above systolic pressure to stop blood flow to the forearm. This is the ischemic part. The patient then exercises the forearm by squeezing something—rolled up towel, a ball, or a dynamometer—repetitively for 2 minutes. After each squeeze, the fingers are extended completely. The exercise is valid when the patient can no longer fully extend the fingers. After 2 minutes, the blood pressure cuff is released (mark time zero) and blood samples are obtained at 1, 3, 5 and 10 minutes and analyzed for lactate, ammonia, pyruvate, creatine kinase, and phosphate. In normal persons, lactate levels increase from 1 mM to 3–5 mM, and ammonia levels rise from 40 μM to 100 μM. In persons with muscle phosphorylase deficiency, lactate hardly rises because the muscles can provide no substrate (glucose) without blood flow. This is diagnostic of glycogenosis, particularly McArdle's disease. Lack of increase in ammonia results from myoadenylate deaminase deficiency.

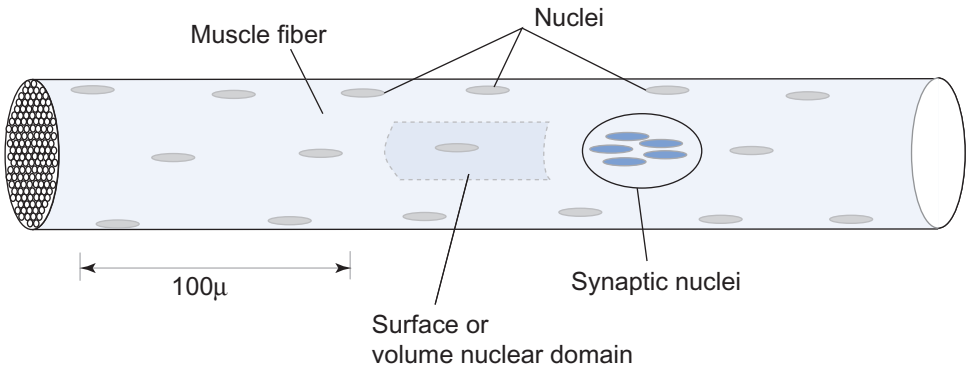

FIGURE 3.7.9 Nuclear and membrane domains in skeletal muscle fibers. Muscle fiber nuclei are located near the periphery of the fiber, nearly aligned in rows with more or less regular spacing with some 35–80 nuclei per mm of fiber. Each nucleus controls protein expression in a volume or surface element called its domain.

Medicine **350**:2682–2688, 2004). Its mode of action is illustrated in Figure 3.7.8.

HUMAN ABILITY TO SWITCH MUSCLE FIBER TYPES IS LIMITED

The overall mechanical and metabolic performance of the muscles is a consequence of the heterogeneous mosaic composition of different muscle fiber types that make up the muscle. One basis of this heterogeneity is the expression of specific myosin isoforms. There are at least 20 structurally distinct classes of myosin heavy chains. Eleven of these are expressed in adult mammalian muscles, but some are specific to one muscle. The most common isoforms are MHCIb, MHCIIa, MHCIIb, and MHCIId.

Immunohistochemistry reveals that some muscle fibers are "pure" types that express only a single myosin heavy chain (MHC) isoform, whereas other muscle fibers contain two or more isoforms and are "hybrids." How can this be? Recall that each muscle fiber contains many nuclei, typically located at the periphery of the cell near the sarcolemma, as shown in Figure 3.7.9. Each nucleus controls a volume of cytoplasm or surface of the fiber called its "**nuclear domain**." A separate population of nuclei congregates near the neuromuscular junction. During transitions between fiber types, it is possible that some of these nuclei receive different signals than others, and therefore transcribe different genes for the expression of myosin. In this way, hybrid muscle fiber types arise. The existence of hybrid muscle fibers allows a more continuous gradation between muscle types, as shown in Table 3.7.5.

Is it possible for humans to convert a type I slow fiber into a type II fast fiber or vice versa? In experimental animals, a fast-twitch muscle removed from its bed and transplanted to a slow-twitch muscle bed converts part way from slow twitch to fast twitch, and vice versa, suggesting that the pattern of neural stimulation determines muscle type. Chronic low-frequency stimulation

TABLE 3.7.5 The Muscle Fiber Type Continuum

Muscle Fiber Type	Myosin Heavy Chain Expression	Muscle Fiber Description
Type I pure fiber	MHCI	Slow
Hybrid	MHCI > MHCIIa	
	MHCIIa > MHCI	
Type IIa pure fiber	MHCIIa	Fast, fatigue resistant
Hybrid	MHCIIa > MHCIIx	
	MHCIIx > MHCIIa	
Type IIx pure fiber	MHCIIx	Fast, fatigable

Hybrid muscle fibers allow transitional forms intermediate between Types I, IIa and IIb. Humans do not make MHCIIb (experimental animals do), so the human form in fast fatiguable muscles is named MHCIIx

of fast-twitch fibers increases the expression of proteins normally expressed only by slow-twitch fibers. Denervation or muscle unloading increases the levels of proteins normally expressed by fast-twitch fibers. Although the evidence is inconclusive, it appears that the stimulation of muscle necessary to transform the fiber types is so severe that no human can train that hard. The consensus seems to be that the transformation of muscle types is limited in part by the original position of the muscle on the muscle fiber-type continuum. The transformation by exercise is always towards a slower type of muscle, but conversion of type IIx fiber to a type I fiber does not occur.

SUMMARY

Muscles produce force or shorten because the actomyosin cross-bridge cycle is activated. This cycle hydrolyzes ATP. Both force and shortening derive their energy from the energy of ATP hydrolysis. Buildup of ADP and Pi slows cross-bridge cycling and reduces the energy available for work. Muscle fibers keep ATP levels high by regenerating ATP through phosphagen buffer systems and metabolism. The first buffer for ATP is creatine phosphate, which rapidly converts ADP to ATP by creatine kinase. Myokinase can convert 2 molecules of ADP to one ATP and one AMP. ATP can also be regenerated from ADP and Pi by glycolysis and by oxidative phosphorylation. Glycolysis makes ATP quickly and anaerobically, but its capacity is low. Oxidative phosphorylation is slower but it has a much larger capacity. During bursts of activity when ATP consumption outstrips oxidative phosphorylation, muscles markedly increase release of lactic acid. Lactic dehydrogenase makes lactic acid from pyruvic acid, simultaneously oxidizing NADH to NAD^+. By regenerating NAD^+, formation of lactic acid allows glycolysis to continue. Lactate is always produced by muscles. The lactate is oxidized within the muscle fibers, or by adjacent oxidative muscle fibers with more mitochondria, or by being exported to the liver where it is used to regenerate glucose. The cycle of blood glucose to muscle glucose to lactic acid to liver and back to blood glucose is called the Cori cycle.

Muscles can burn carbohydrates, fats, and proteins for energy. Which fuel is used depends on the duration and intensity of exercise. Rapid bursts of high activity are generally fueled by glycolysis, whereas slower activity lasting for long periods relies on oxidation of fats. Exercise increases the Glut4 carriers in the muscle to increase their glucose uptake independently of insulin.

Muscles are made up of thousands of muscle fibers that can be grouped into a few kinds of muscle fibers. These have different contractile and metabolic characteristics and express particular isoforms of a variety of muscle proteins. The type I muscle fiber is a slow-twitch fiber that typically contains a slow myosin isoform but contains lots of mitochondria and myoglobin in the cytoplasm. It expresses a slow-twitch SR Ca-ATPase and its TnC has only one regulatory Ca^{2+}-binding site. Type I fibers are oxidative and fatigue resistant. Type II fibers are fast-twitch fibers and there are two main varieties: type IIa fibers are fast oxidative fibers that contain SERCA1a SR pumps and TnC_2, which has two Ca^{2+} regulatory binding sites. Type IIb fibers are fast and glycolytic. Type I and IIa fibers contribute endurance and some speed; type IIb fibers contribute speed and power.

Fatigue is the transient loss in muscle work capacity or strength that results from preceding work. In humans, most fatigue originates in the muscle, as opposed to the brain. There are two types of fatigue: the fatigue that rapidly accompanies the use of maximal force, which can be sustained only for seconds and the fatigue that results from repetitive submaximal contractions such as long-distance running. Generally, fatigue is delayed longer with less strenuous activity. Fatigue has two origins: central fatigue is the reduction in nervous excitation and peripheral fatigue originates in the muscle. The fatigue that accompanies maximum force is due to buildup of Pi that originates from creatine phosphate. Endurance fatigue has both central and peripheral components. The peripheral component is due to depletion

of glycogen, most likely that part of glycogen that determines Ca^{2+} release from the SR.

Training can improve fatigue resistance by fine-tuning muscle fiber metabolism and increasing muscle size. Maximal muscle force depends only on muscle size and is increased by resistance training—few repetitions against high resistance. Endurance training increases muscle capillarity, mitochondrial volume, and with proper nutrition, glycogen stores. Although muscle types can be converted in laboratory animals, it is unlikely that humans can substantially alter their muscle types by training. Muscles are heterogeneous with respect to muscle fiber types. They generally contain some population of type I, IIa, and IIb fibers and this distribution varies from person to person.

REVIEW QUESTIONS

1. What happens if ATP is not regenerated during muscle contraction?
2. What reactions consume ATP during muscular activity? Which of these consumes most of the ATP?
3. What does creatine kinase do? What does myokinase do? If ATP is regenerated by creatine kinase, what happens to cytoplasmic [Pi]? If ATP is regenerated by myokinase, what happens to cytoplasmic [AMP]?
4. How do fatty acids produce ATP in muscle? Is oxygen necessary for this process?
5. How does glucose produce ATP in muscle? Is oxygen necessary for this process?
6. Why do muscles make lactic acid? What happens to the lactic acid that muscles make? Why do muscles make more lactic acid during vigorous activity?
7. What is glycogenolysis? What does it produce in muscle? Can muscle contribute to blood glucose? Why or why not?
8. How does the liver help in the energy supply of muscle during exercise?
9. What does exercise do to glucose uptake by muscles? Does this effect require insulin?
10. What causes fatigue at high recruitment, short duration? What causes fatigue at low intensity, long duration?
11. Why does a deficiency in muscle phosphorylase cause exercise intolerance?
12. Describe the characteristics of type I, type IIa, and type IIb muscles. Can these be transformed by training?