Metabolism Regulation 3

The role of ATP in metabolic pathways

ATP Has Two Metabolic Roles

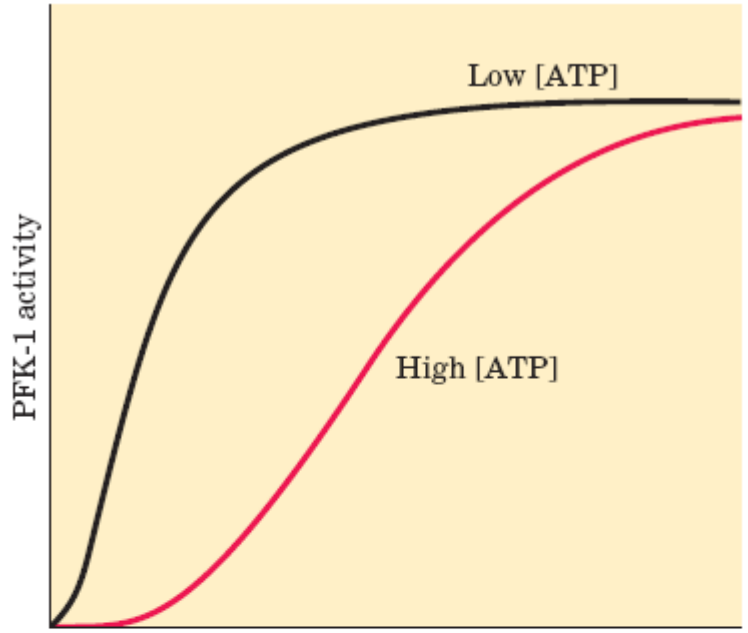
The role of ATP in metabolism is twofold:

1. It serves in a stoichiometric role to establish large equilibrium constants for metabolic conversions and to render metabolic sequences thermodynamically favorable.

This is the role referred to when we call ATP the energy currency of the cell.

2. ATP also serves as an important allosteric effector in the kinetic regulation of metabolism.

Its concentration (relative to those of ADP and AMP) is an index of the energy status of the cell and determines the rates of regulatory enzymes situated at key points in metabolism, such as PFK in glycolysis and FBPase in gluconeogenesis.



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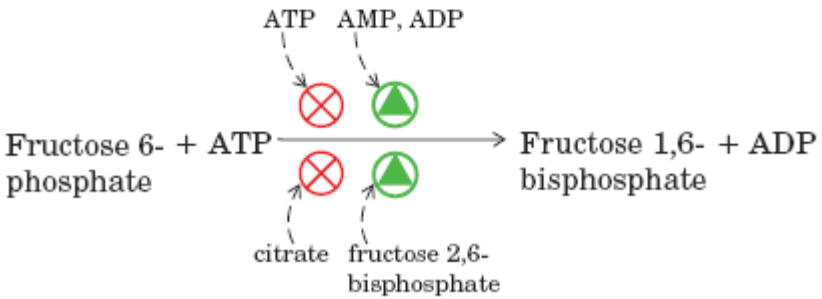

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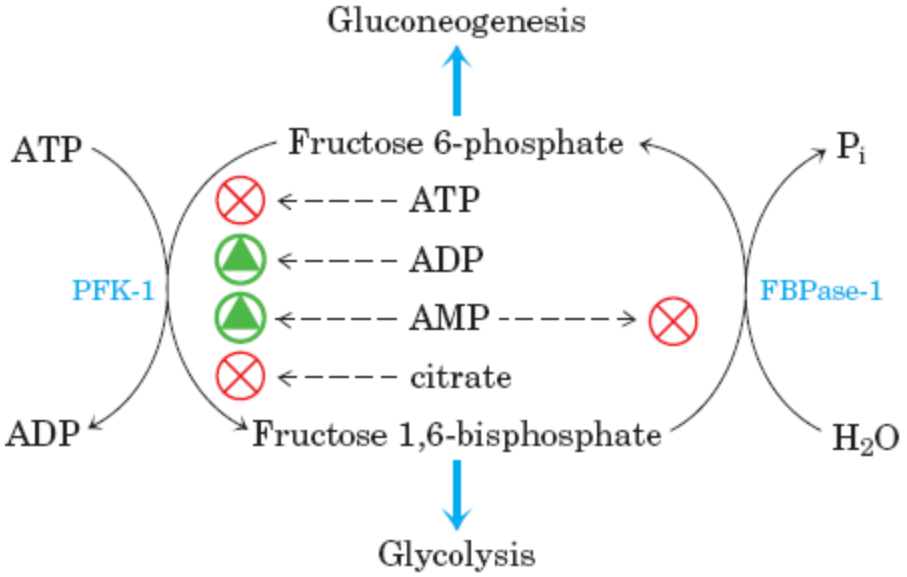


FIGURE 15–21 Regulation of fructose 1,6-bisphosphatase-1 (FBPase-1) and phosphofructokinase-1 (PFK-1). The important role of fructose 2,6-bisphosphate in the regulation of this substrate cycle is detailed in subsequent figures.

Is There a Good Index of Cellular Energy Status?

- Energy transduction and energy storage in the *adenylate system*—ATP, ADP, and AMP—lie at the very heart of metabolism.
- ATP, ADP, and AMP are all important effectors in exerting kinetic control on regulatory enzymes situated at key points in metabolism, so uncontrolled changes in their concentrations could have drastic consequences.
- The regulation of metabolism by adenylates in turn requires close control of the relative concentrations of ATP, ADP, and AMP.
- Some ATP-consuming reactions produce ADP; PFK and hexokinase are examples. Others lead to the formation of AMP, as in fatty acid activation by acyl-CoA synthetases:

Fatty acid + ATP + coenzyme A → AMP + PPi + fatty acyl-CoA

Is There a Good Index of Cellular Energy Status?

Adenylate Kinase Interconverts ATP, ADP, and AMP

- *Adenylate kinase*, by catalyzing the reversible phosphorylation of AMP by ATP, provides a direct connection among all three members of the adenylate pool:

$$ATP + AMP \leftrightarrow 2\ ADP$$

- The free energy of hydrolysis of a phosphoanhydride bond is essentially the same in ADP and ATP, and the standard free energy change for this reaction is close to zero.

Is There a Good Index of Cellular Energy Status?

- Energy Charge Relates the ATP Levels to the Total Adenine Nucleotide Pool

- The role of the adenylate system is to provide phosphoryl groups at high group-transfer potential in order to drive thermodynamically unfavorable reactions. The capacity of the adenylate system to fulfill this role depends on how fully charged it is with phosphoric anhydrides. Energy charge is an index of this capacity:

$$\text{Energy charge} = \frac{1}{2}\left(\frac{2\,[\text{ATP}] + [\text{ADP}]}{[\text{ATP}] + [\text{ADP}] + [\text{AMP}]}\right)$$

- The denominator represents the total adenylate pool ([ATP] +[ADP] + [AMP]); the numerator is the number of phosphoric anhydride bonds in the pool, two for each ATP and one for each ADP. The factor ½ normalizes the equation so that energy charge, or **E.C.,** has the range 0 to 1.0.

- If all the adenylate is in the form of ATP, E.C. = 1.0, and the potential for phosphoryl transfer is maximal.

- At the other extreme, if AMP is the only adenylate form present, E.C. = 0. It is reasonable to assume that the adenylate kinase reaction is never far from equilibrium in the cell. Then the relative amounts of the three adenine nucleotides are fixed by the energy charge.

Is There a Good Index of Cellular Energy Status?

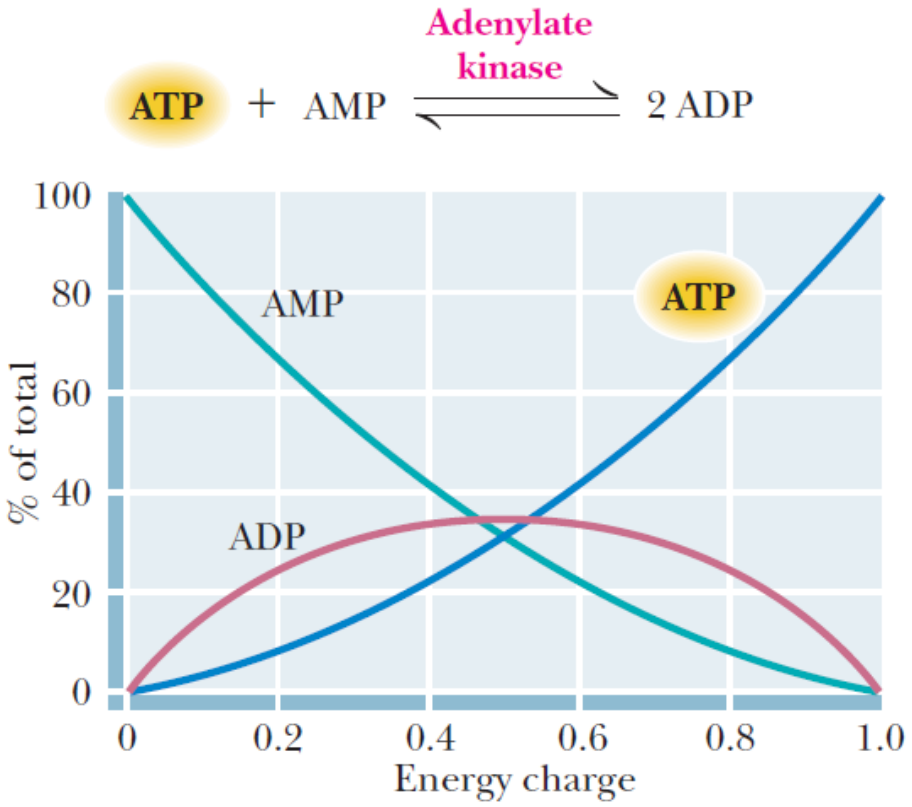


FIGURE 27.2 Relative concentrations of AMP, ADP, and ATP as a function of energy charge. (This graph was constructed assuming that the adenylate kinase reaction is at equilibrium and that $\Delta G^{\circ\prime}$ for the reaction is −473 J/mol; $K_{eq} = 1.2$.)

Figure 27.2 shows the relative changes in the concentrations of the adenylates as energy charge varies from 0 to 1.0.

Is There a Good Index of Cellular Energy Status?

Key Enzymes Are Regulated by Energy Charge

- Regulatory enzymes typically respond in reciprocal fashion to adenine nucleotides. For example, PFK is stimulated by AMP and inhibited by ATP. If the activities of various regulatory enzymes are examined in vitro as a function of energy charge, an interesting relationship appears. Regulatory enzymes in energy-producing catabolic pathways show greater activity at low energy charge, but the activity falls off abruptly as E.C. approaches 1.0. In contrast, regulatory enzymes of anabolic sequences are not very active at low energy charge, but their activities increase exponentially as E.C. nears 1.0. These contrasting responses are termed **R,** for ATP-regenerating, and **U,** for ATP-utilizing (Figure 27.3).

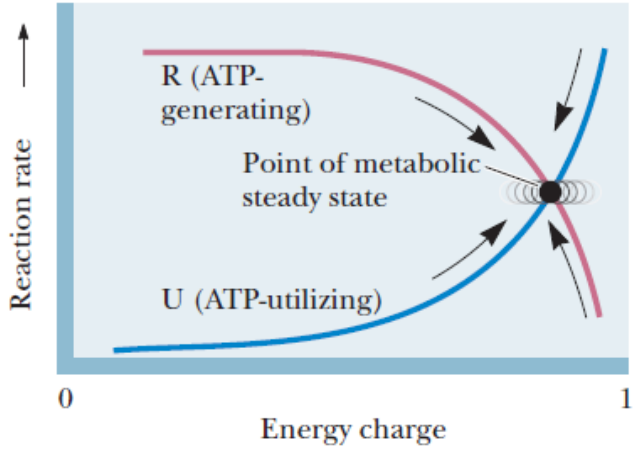


FIGURE 27.3 Responses of regulatory enzymes to variation in energy charge.

Is There a Good Index of Cellular Energy Status?

- Regulatory enzymes such as PFK and pyruvate kinase in glycolysis follow the **R** response curve as E.C. is varied. Note that PFK itself is an ATP-utilizing enzyme, using ATP to phosphorylate fructose-6-phosphate to yield fructose-1,6-bisphosphate. Nevertheless, because PFK acts physiologically as the valve controlling the flux of carbohydrate down the catabolic pathways of cellular respiration that lead to ATP regeneration, it responds as an **"R"** enzyme to energy charge.
- Regulatory enzymes in anabolic pathways, such as acetyl-CoA carboxylase, which initiates fatty acid biosynthesis, respond as **"U"** enzymes.
- The overall purposes of the **R** and **U** pathways are diametrically opposite in terms of ATP involvement. Note in Figure 27.3 that the **R** and **U** curves intersect at a rather high E.C. value. As E.C. increases past this point, **R** activities decline precipitously and U activities rise. That is, when E.C. is very high, biosynthesis is accelerated while catabolism diminishes. The consequence of these effects is that ATP is used up faster than it is regenerated, and so E.C. begins to fall. As E.C. drops below the point of intersection, R processes are favored over U. Then, ATP is generated faster than it is consumed, and E.C. rises again. The net result is that the value of energy charge oscillates about a point of steady state (Figure 27.3). The experimental results obtained from careful measurement of the relative amounts of AMP, ADP, and ATP in living cells reveals that normal cells have an energy charge in the neighborhood **of 0.85 to 0.88**. Maintenance of this steady-state value is one criterion of cell health and normalcy.

Is There a Good Index of Cellular Energy Status?

Phosphorylation Potential Is a Measure of Relative ATP Levels

- Because energy charge is maintained at a relatively constant value in normal cells, it is not an informative index of cellular capacity to carry out phosphorylation reactions. The relative concentrations of ATP, ADP, and P_i do provide such information, and a function called **phosphorylation potential** has been defined in terms of these concentrations:

$$ADP + P_i \leftrightarrow ATP + H_2O$$

- Phosphorylation potential, G, is equal to [ATP]/([ADP][P_i]). Note that this expression includes a term for the concentration of inorganic phosphate. [P_i] has substantial influence on the thermodynamics of ATP hydrolysis.
- In contrast with energy charge, phosphorylation potential varies over a significant range as the actual proportions of ATP, ADP, and P_i in cells vary in response to metabolic state.
- G ranges from 200 to 800 M_{21}, or more, with higher levels signifying more ATP and correspondingly greater phosphorylation potential.

How Is Overall Energy Balance Regulated in Cells?

- **AMP-activated protein kinase (AMPK)** is the cellular energy sensor.
- When cellular energy levels are high, as signaled by high ATP concentrations, AMPK is inactive. When cellular energy levels are depleted, as signaled by high [AMP], AMPK is allosterically activated and phosphorylates many targets controlling cellular energy production and consumption.
- Recall that, due to the nature of the adenylate kinase equilibrium, AMP levels increase exponentially as ATP levels decrease. AMP is an allosteric activator of AMPK, whereas ATP at high levels acts as an allosteric inhibitor by displacing AMP from the allosteric site. Thus, competition between AMP and ATP for binding to the AMPK allosteric sites determines the activity of AMPK.

How Is Overall Energy Balance Regulated in Cells?

- Activation of AMPK (1) sets in motion catabolic pathways leading to ATP synthesis and (2) shuts down pathways that consume ATP energy, such as biosynthesis and cell growth.

How Is Overall Energy Balance Regulated in Cells?

AMPK Targets Key Enzymes in Energy Production and Consumption

- Activation of AMPK leads to phosphorylation of many key enzymes in energy metabolism.
- Those involved in energy production that are activated upon phosphorylation by AMPK include phosphofructokinase-2 (PFK-2). In contrast to protein kinase A phosphorylation of PFK-2, AMPK phosphorylation of liver PFK-2 enhances fructose-2,6-bisphosphate synthesis, which in turn stimulates glycolysis.
- Enzymes involved in energy consumption that are down-regulated upon phosphorylation by AMPK include glycogen synthase, acetyl-CoA carboxylase (which catalyzes the committed step in fatty acid biosynthesis), and 3-hydroxy-3-methylglutaryl-CoA reductase, which carries out the key regulatory reaction in cholesterol biosynthesis. Further, AMPK phosphorylation of various transcription factors leads to diminished expression of genes encoding biosynthetic enzymes and elevated expression of catabolic genes. Activation of AMPK also enhances energy production by promoting mitochondrial biogenesis.

How Is Overall Energy Balance Regulated in Cells?

AMPK Controls Whole-Body Energy Homeostasis

- Beyond these cellular effects, AMPK plays a central role in energy balance in multicellular organisms (Figure 27.6).
- AMPK in skeletal muscle is activated by hormones such as adiponectin and leptin, adipocyte-derived hormones that govern eating behavior and energy homeostasis.
- Physical activity (exercise) also activates muscle AMPK. In turn, skeletal muscle AMPK activates glucose uptake, fatty acid oxidation, and mitochondrial biogenesis through its phosphorylation of metabolic enzymes and transcription factors that control expression of genes involved in energy production and consumption.
- AMPK's actions in the liver lead to lowered ATP (energy) consumption through down-regulation of fatty acid synthesis, cholesterol synthesis, and gluconeogenesis.
- **Metformin,** a widely used drug for the treatment of type 2 diabetes, lowers blood glucose levels through inhibition of liver gluconeogenesis; metformin achieves this result through activation of AMPK.
- AMPK blocks insulin secretion by pancreatic *b*-cells; insulin is a hormone that favors energy storage (glycogen and fat synthesis).
- AMPK is also a master regulator of eating behavior through its activity in the hypothalamus, the key center for regulation of food intake.

How Is Overall Energy Balance Regulated in Cells?

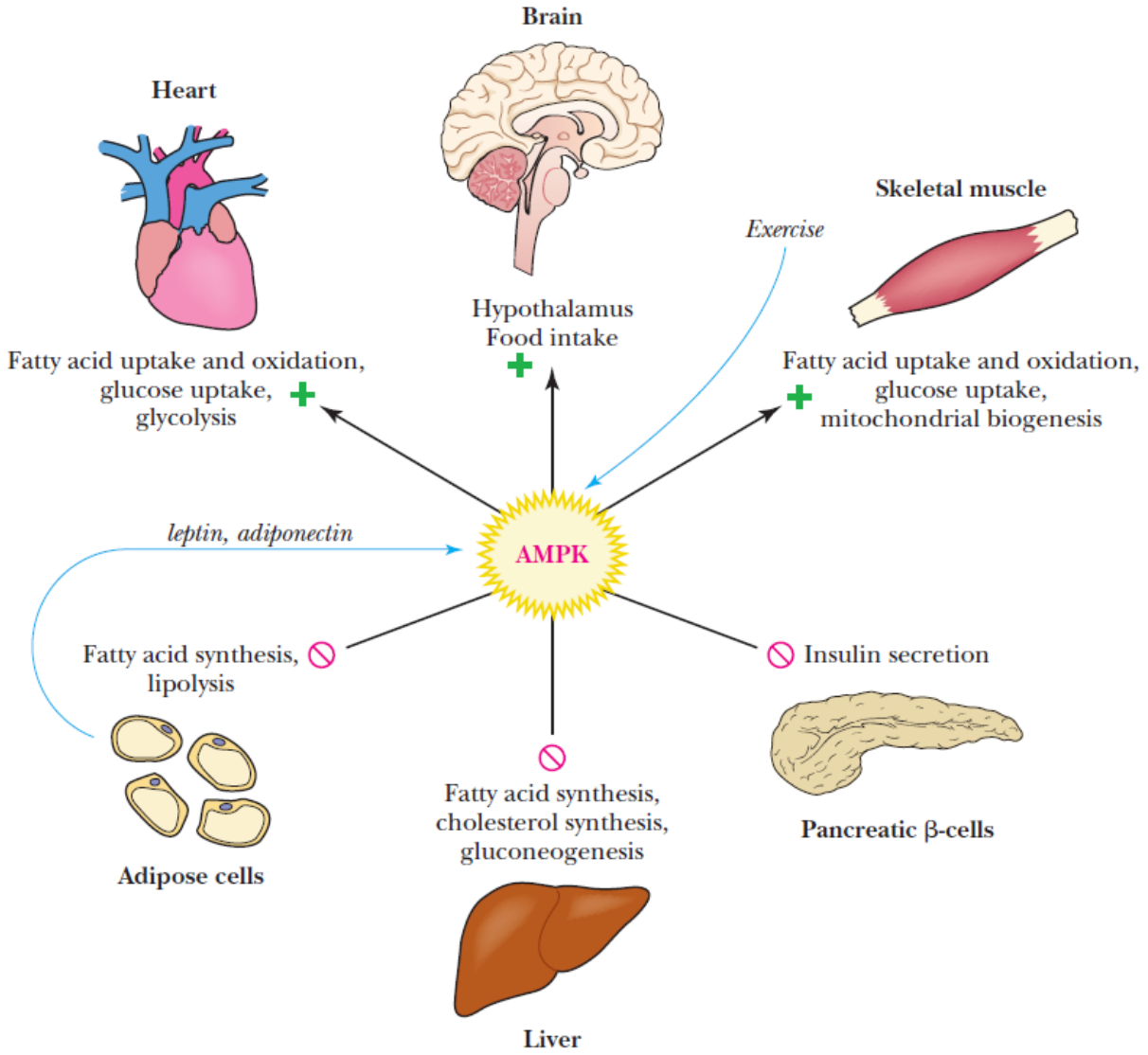


FIGURE 27.6 AMPK regulation of energy production and consumption in mammals. (Adapted from Figure 1 in Kahn, B. B., Alquier, T., Carling, D., and Hardie, D. G., 2005. AMP-activated protein kinase: Ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metabolism* **1**:15–25.)

How Is Metabolism Integrated in a Multicellular Organism?

- In complex multicellular organisms, organ systems have arisen to carry out specific physiological functions. Each organ expresses a repertoire of metabolic pathways that is consistent with its physiological purpose. Such specialization depends on coordination of metabolic responsibilities among organs so that the organism as a whole may thrive.

- Essentially all cells in animals have the set of enzymes common to the central pathways of intermediary metabolism, especially the enzymes involved in the formation of ATP and the synthesis of glycogen and lipid reserves. Nevertheless, organs differ in the metabolic fuels they prefer as substrates for energy production. Important differences also occur in the ways ATP is used to fulfill the organs' specialized metabolic functions.

- To illustrate these relationships, we will consider the metabolic interactions among the major organ systems found in humans: brain, skeletal muscle, heart, adipose tissue, and liver. In particular, the focus will be on energy metabolism in these organs (Figure 27.7).

- The major fuel depots in animals are *glycogen in liver and muscle*; *triacylglycerols (fats) stored in adipose tissue*; and protein, most of which is in skeletal muscle. In general, the order of preference for the use of these fuels is the order given: glycogen . Triacylglycerol . protein.

- Nevertheless, the tissues of the body work together to maintain **energy homeostasis (caloric homeostasis),** defined as *a constant availability of fuels in the blood*.

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles

Table 27.1 summarizes the energy metabolism of the major human organs.

TABLE 27.1 Energy Metabolism in Major Vertebrate Organs

Organ	Energy Reservoir	Preferred Substrate	Energy Sources Exported
Brain	None	Glucose (ketone bodies during starvation)	None
Skeletal muscle (resting)	Glycogen	Fatty acids	None
Skeletal muscle (strenuous exercise)	None	Glucose from glycogen	Lactate
Heart muscle	Glycogen	Fatty acids	None
Adipose tissue	Triacylglycerol	Fatty acids	Fatty acids, glycerol
Liver	Glycogen, triacylglycerol	Amino acids, glucose, fatty acids	Fatty acids, glucose, ketone bodies

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles (**Brain**)

- **Brain:** The brain has two remarkable metabolic features. First, it has a very high respiratory metabolism. In resting adult humans, 20% of the oxygen consumed is used by the brain, even though it constitutes only 2% or so of body mass. Interestingly, this level of oxygen consumption is independent of mental activity, continuing even during sleep. Second, the brain is an organ with no significant fuel reserves—no glycogen, expendable protein, or fat (even in "fatheads"!). Normally, the brain uses only glucose as a fuel and is totally dependent on the blood for a continuous, incoming supply. Interruption of glucose supply for even brief periods of time (as in a stroke) can lead to irreversible losses in brain function.

- The brain uses glucose to carry out ATP synthesis via cellular respiration. High rates of ATP production are necessary to power the plasma membrane Na^+K^+-ATPase so that the membrane potential essential for transmission of nerve impulses is maintained.

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles (**Brain**)

- During prolonged fasting or starvation, the body's glycogen reserves are depleted. Under such conditions, the brain adapts to use *β*-hydroxybutyrate as a source of fuel, converting it to acetyl-CoA for energy production via the citric acid cycle.
- *β* -Hydroxybutyrate is formed from fatty acids in the liver. Although the brain cannot use free fatty acids or lipids directly from the blood as fuel, the conversion of these substances to *β*-hydroxybutyrate in the liver allows the brain to use body fat as a source of energy.
- The brain's other potential source of fuel during starvation is glucose obtained from gluconeogenesis in the live, using the carbon skeletons of amino acids derived from muscle protein breakdown.
- The adaptation of the brain to use *β* -hydroxybutyrate from fat spares protein from degradation until lipid reserves are exhausted.

How Is Metabolism Integrated in a Multicellular Organism?

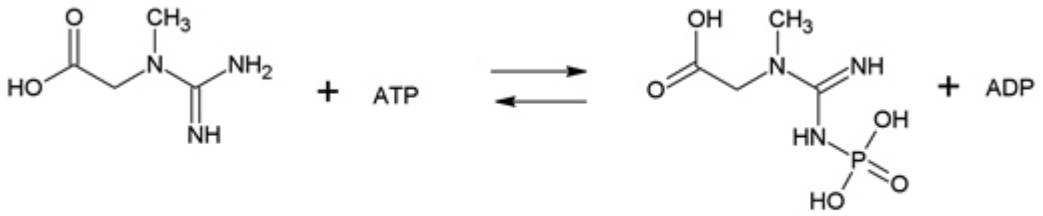
The Major Organ Systems Have Specialized Metabolic Roles (**Muscle**)

- **Muscle:** Skeletal muscle is responsible for about 30% of the O_2 consumed by the human body at rest. During periods of maximal exertion, skeletal muscle can account for more than 90% of the total metabolism.

- Muscle metabolism is primarily dedicated to the production of ATP as the source of energy for contraction and relaxation. Muscle contraction occurs when a motor nerve impulse causes Ca^{2+} release from specialized endomembrane compartments (the transverse tubules and sarcoplasmic reticulum). Ca^{2+} floods the *sarcoplasm* (the term denoting the cytosolic compartment of muscle cells), where it binds to **troponin C,** a regulatory protein, initiating a series of events that culminate in the sliding of myosin thick filaments along actin thin filaments. This mechanical movement is driven by energy released upon hydrolysis of ATP. The net result is that the muscle shortens. Relaxation occurs when the Ca^{2+} ions are pumped back into the sarcoplasmic reticulum by the action of a Ca^{2+}-transporting membrane ATPase. Two Ca^{2+} ions are translocated per ATP hydrolyzed. The amount of ATP used during relaxation is almost as much as that consumed during contraction.

- Because muscle contraction is an intermittent process that occurs upon demand, muscle metabolism is designed for a demand response.

- Muscle at rest uses free fatty acids, glucose, or ketone bodies as fuel and produces ATP via oxidative phosphorylation. Resting muscle also contains about 2% glycogen and about 0.08% phosphocreatine by weight. When ATP is used to drive muscle contraction, the ADP formed can be reconverted to ATP by *creatine kinase* at the expense of phosphocreatine. Muscle phosphocreatine can generate enough ATP to power about 4 seconds of exertion.



Creatine Phosphocreatine

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles (**Muscle**)

- During strenuous exertion, such as a 100-meter sprint, once the phosphocreatine is depleted, muscle relies solely on its glycogen reserves, making the ATP for contraction via glycolysis. In contrast with the citric acid cycle and oxidative phosphorylation pathways, glycolysis is capable of explosive bursts of activity, and the flux of glucose-6-phosphate through this pathway can increase 2000-fold almost instantaneously. The triggers for this activation are Ca^{2+} and the “fight or flight” hormone *epinephrine.* Little interorgan cooperation occurs during strenuous (anaerobic) exercise.

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles (**Muscle**)

- Muscle fatigue is the inability of a muscle to maintain power output. During maximum exertion, the onset of fatigue takes only 20 seconds or so. Fatigue is not the result of exhaustion of the glycogen reserves, nor is it a consequence of lactate accumulation in the muscle. Instead, it is caused by a decline in intramuscular pH as protons are generated during glycolysis. (The overall conversion of glucose to 2 lactate in glycolysis is accompanied by the release of 2 H+.) The pH may fall as low as 6.4. It is likely that the decline in PFK activity at low pH leads to a lowered flux of hexose through glycolysis and inadequate ATP levels, causing a feeling of fatigue. One benefit of PFK inhibition is that the ATP remaining is not consumed in the PFK reaction, thereby sparing the cell from the more serious consequences of losing all of its ATP.

- During fasting or excessive activity, skeletal muscle protein is degraded to amino acids so that their carbon skeletons can be used as fuel. Many of the skeletons are converted to pyruvate, which can be transaminated back into alanine for export via the circulation. Alanine is carried to the liver, which in turn deaminates it back into pyruvate so that it can serve as a substrate for gluconeogenesis. Although muscle protein can be mobilized as an energy source, it is not efficient for an organism to consume its muscle and lower its overall fitness for survival. Muscle protein represents a fuel of last resort.

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles (**Heart**)

- **Heart:** In contrast with the intermittent work of skeletal muscle, *the activity of heart muscle is constant and rhythmic*. The range of activity in heart is also much less than that in muscle. Consequently, the heart functions as a completely aerobic organ and, as such, is very rich in mitochondria. Roughly half the cytoplasmic volume of heart muscle cells is occupied by mitochondria. Under normal working conditions, the heart prefers fatty acids as fuel, oxidizing acetyl-CoA units via the citric acid cycle and producing ATP for contraction via oxidative phosphorylation.
- Heart tissue has minimal energy reserves: a small amount of phosphocreatine and limited quantities of glycogen. As a result, the heart must be continually nourished with oxygen and free fatty acids, glucose, or ketone bodies as fuel.

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles (**Adipose tissue**)

- **Adipose Tissue:** Adipose tissue is an amorphous tissue that is widely distributed about the body—*around blood vessels*, *in the abdominal cavity* and *mammary glands*, and most prevalently, as deposits *under the skin*.
- Long considered merely a storage depot for fat, adipose tissue is now appreciated as an endocrine organ responsible for secretion of a variety of hormones that govern eating behavior and caloric homeostasis.
- It consists principally of cells known as adipocytes that no longer replicate. However, adipocytes can increase in number as adipocyte precursor cells divide, and obese individuals tend to have more of them. As much as 65% of the weight of adipose tissue is triacylglycerol that is stored in adipocytes, essentially as oil droplets.
- The average 70-kg man has enough caloric reserve stored as fat to sustain a 6000 kJ/day rate of energy production for 3 months, which is adequate for survival, assuming no serious metabolic aberrations (such as nitrogen, mineral, or vitamin deficiencies). Despite their role as energy storage depots, adipocytes have a high rate of metabolic activity, synthesizing and breaking down triacylglycerol so that the average turnover time for a triacylglycerol molecule is just a few days.

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles (**Adipose Tissue**)

- Adipocytes actively carry out cellular respiration, transforming glucose to energy via glycolysis, the citric acid cycle, and oxidative phosphorylation.
- If glucose levels in the diet are high, glucose is converted to acetyl-CoA for fatty acid synthesis.
- However, under most conditions, free fatty acids for triacylglycerol synthesis are obtained from the liver. Because adipocytes lack glycerol kinase, they cannot recycle the glycerol of triacylglycerol but rather depend on glycolytic conversion of glucose to dihydroxyacetone-3-phosphate (DHAP) and the reduction of DHAP to glycerol-3-phosphate for triacylglycerol biosynthesis.
- Adipocytes also require glucose to feed the pentose phosphate pathway for NADPH production.
- Glucose plays a pivotal role for adipocytes. If glucose levels are adequate, glycerol-3-phosphate is formed in glycolysis and the free fatty acids liberated in triacylglycerol breakdown are re-esterified to glycerol to re-form triacylglycerols. However, if glucose levels are low, [glycerol-3-phosphate] falls and free fatty acids are released to the bloodstream.

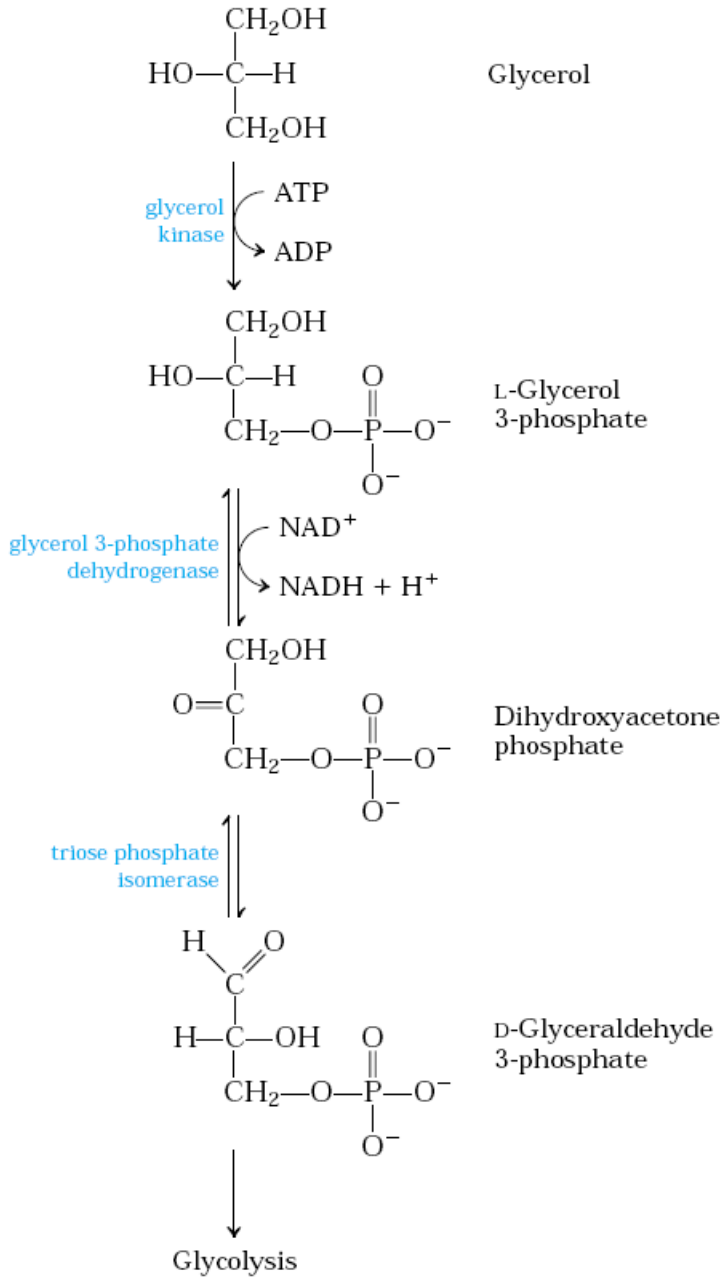


FIGURE 17–4 Entry of glycerol into the glycolytic pathway.

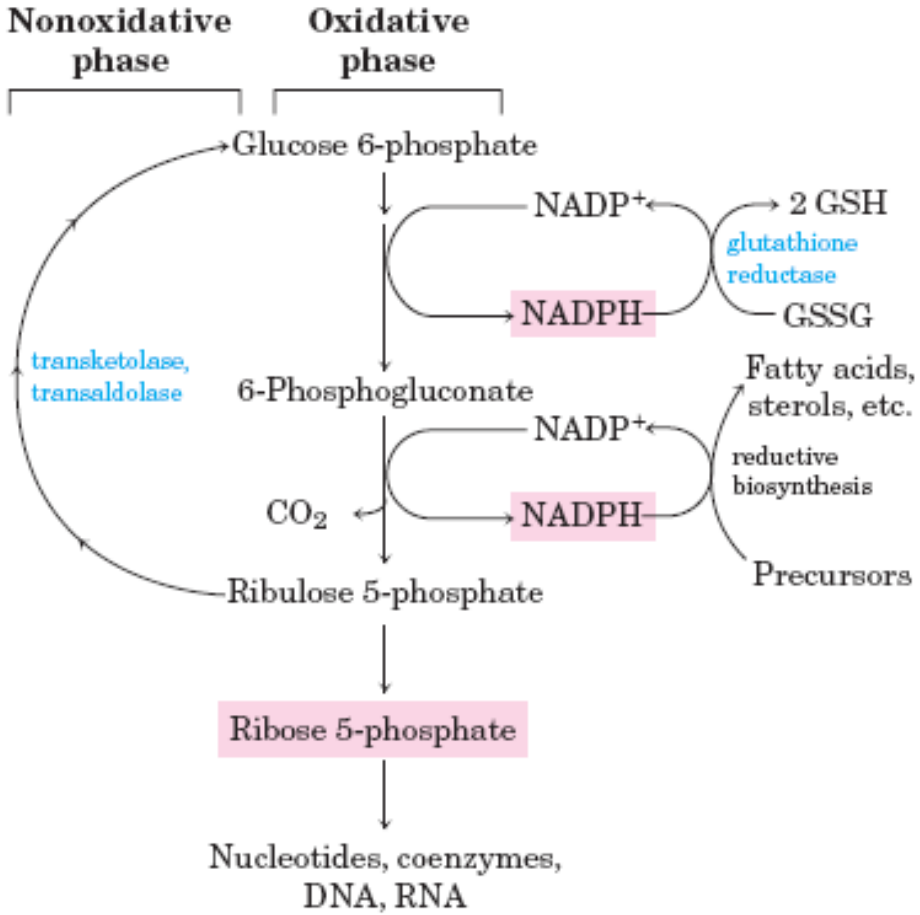


FIGURE 14–20 **General scheme of the pentose phosphate pathway.** NADPH formed in the oxidative phase is used to reduce glutathione, GSSG (see Box 14–3) and to support reductive biosynthesis. The other product of the oxidative phase is ribose 5-phosphate, which serves as precursor for nucleotides, coenzymes, and nucleic acids. In cells that are not using ribose 5-phosphate for biosynthesis, the nonoxidative phase recycles six molecules of the pentose into five molecules of the hexose glucose 6-phosphate, allowing continued production of NADPH and converting glucose 6-phosphate (in six cycles) to CO_2.

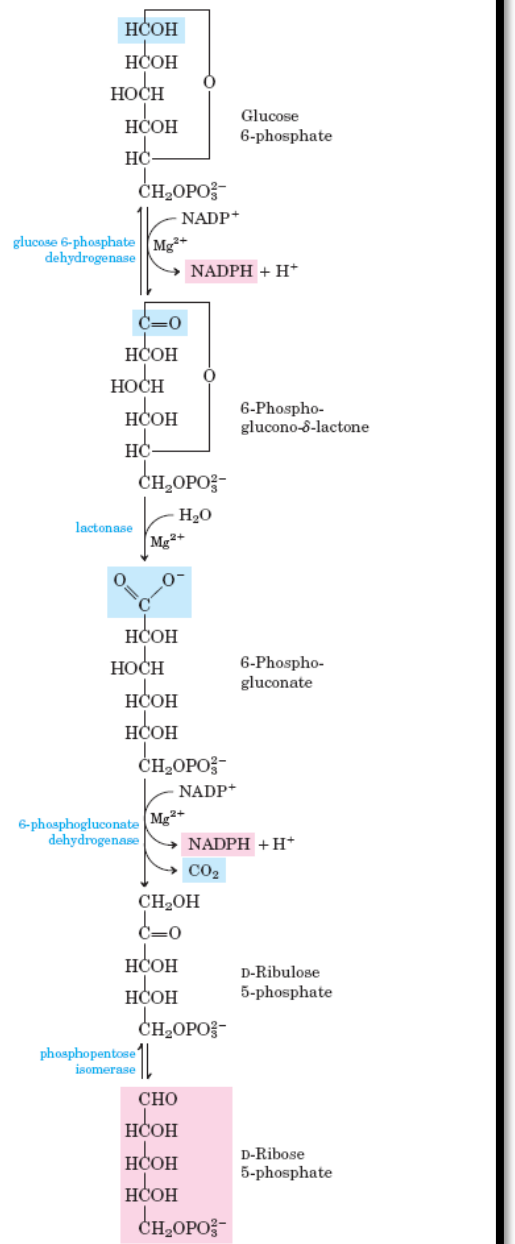


FIGURE 14–21 **Oxidative reactions of the pentose phosphate pathway.** The end products are ribose 5-phosphate, CO_2, and NADPH.

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles (**Adipose Tissue**)

- *"Brown Fat"* A specialized type of adipose tissue, so-called **brown fat,** is found in newborns and hibernating animals. The abundance of mitochondria, which are rich in cytochromes, is responsible for the brown color of this fat. As usual, these mitochondria are very active in electron transport–driven proton translocation, but these particular mitochondria contain in their inner membranes a protein, **thermogenin,** also known as *uncoupling protein 1 (UCP1)*, that creates a passive proton channel, permitting the H^+ ions to reenter the mitochondrial matrix without generating ATP. Instead, the energy of oxidation is dissipated as heat. Indeed, brown fat is specialized to oxidize fatty acids for heat production rather than ATP synthesis.

Brown adipose tissue in infants. At birth, human infants have brown fat distributed as shown here, to protect the spine, major blood vessels, and internal organs.

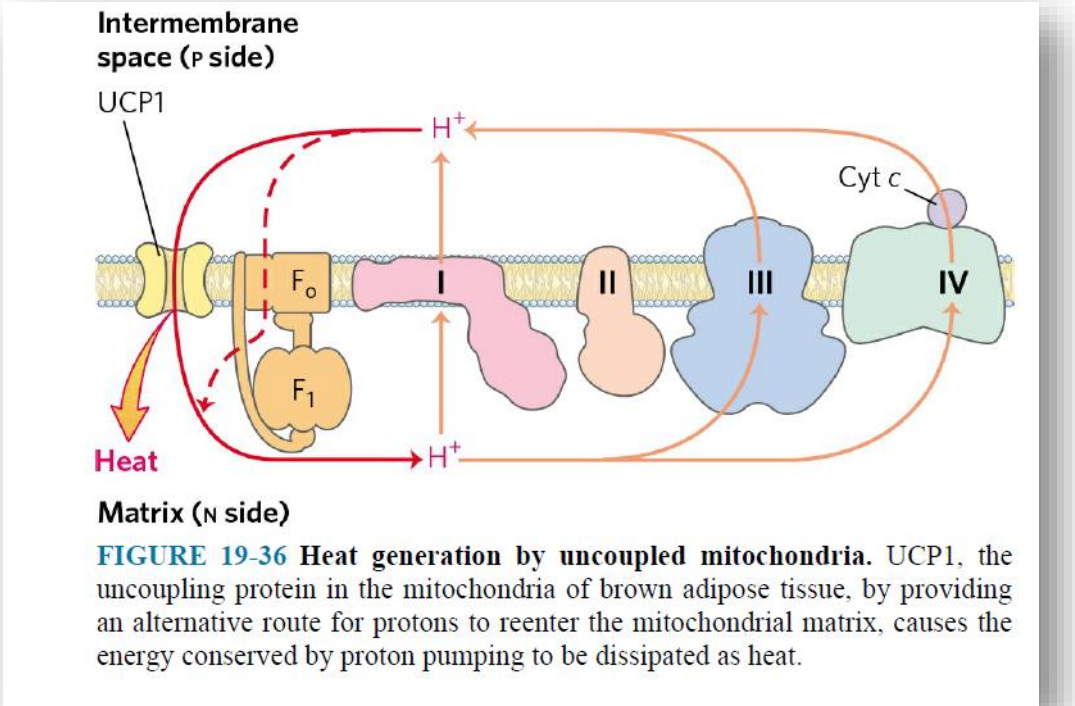


FIGURE 19-36 Heat generation by uncoupled mitochondria. UCP1, the uncoupling protein in the mitochondria of brown adipose tissue, by providing an alternative route for protons to reenter the mitochondrial matrix, causes the energy conserved by proton pumping to be dissipated as heat.

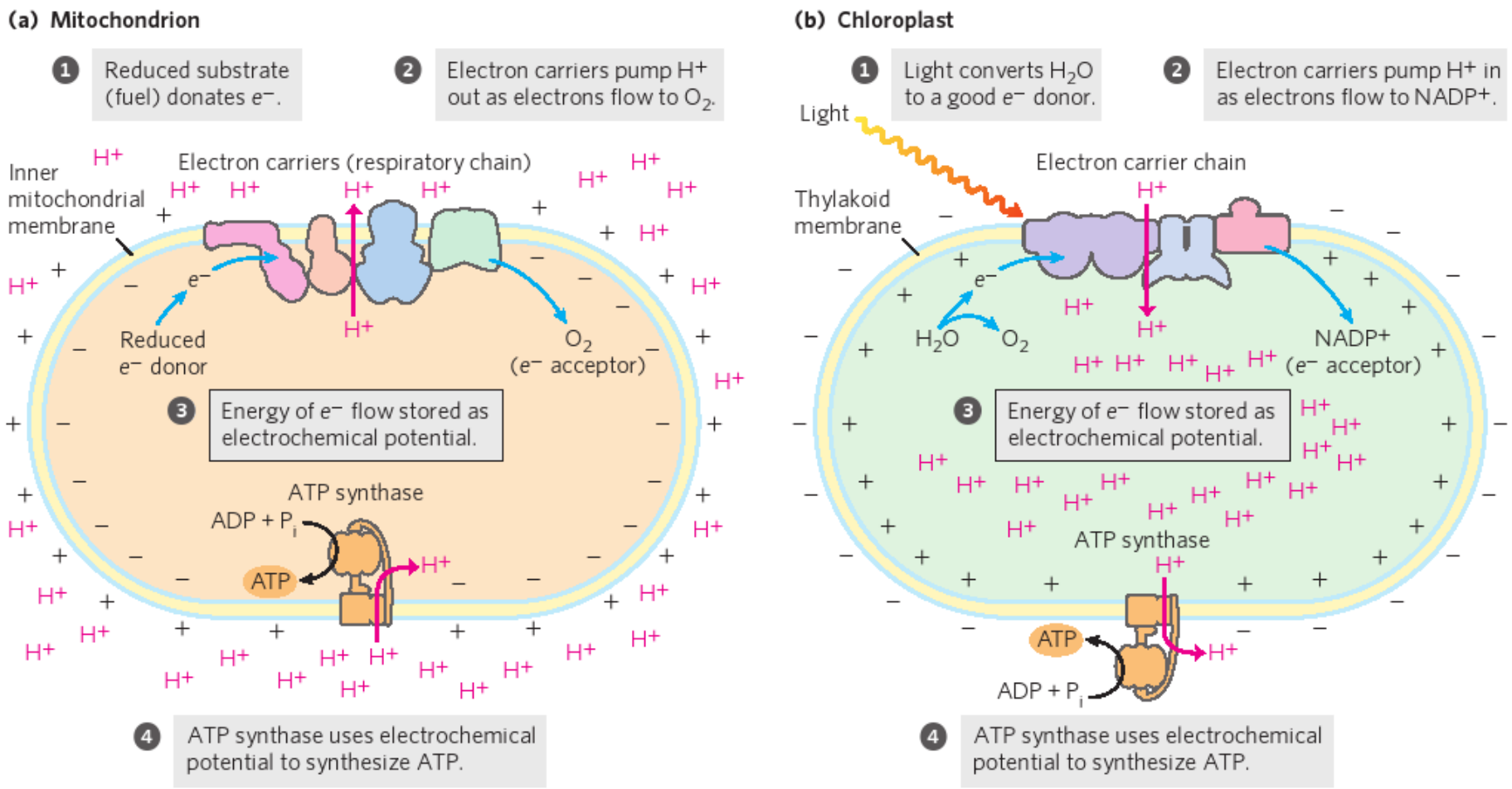


FIGURE 19–1 The chemiosmotic mechanism for ATP synthesis. (a) In mitochondria, electrons move through a chain of membrane-bound carriers (the respiratory chain) spontaneously, driven by the high reduction potential of oxygen and the relatively low reduction potentials of the various reduced substrates (fuels) that undergo oxidation in the mitochondrion. **(b)** In chloroplasts, the movement of electrons through a chain of membrane-bound carriers is driven by the energy of photons absorbed by the green pigment chlorophyll. In both organelles, electron flow creates an electrochemical potential by the transmembrane movement of protons and positive charge. In both cases this electrochemical potential drives ATP synthesis by a membrane-bound enzyme, ATP synthase, that is fundamentally similar in both mitochondria and chloroplasts, and in bacteria and archaea as well.

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles (**liver**)

- **Liver:** The liver serves as the major metabolic processing center in vertebrates. Except for dietary triacylglycerols, which are metabolized principally by adipose tissue, most of the incoming nutrients that pass through the intestinal tract are routed via the portal vein to the liver for processing and distribution.

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles (**liver**)

- Much of the liver's activity centers around conversions involving glucose-6-phosphate. Glucose-6-phosphate can be converted to glycogen, released as blood glucose, used to generate NADPH and pentoses via the pentose phosphate cycle, or catabolized to acetyl-CoA for fatty acid synthesis or for energy production via oxidative phosphorylation. Most of the liver glucose-6-phosphate arises from dietary carbohydrate, from degradation of glycogen reserves, or from muscle lactate that enters the gluconeogenic pathway.

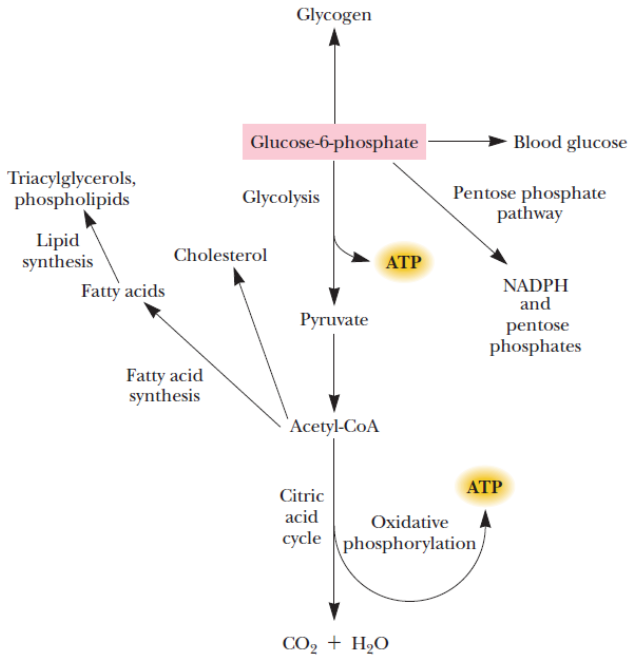


FIGURE 27.11 Metabolic conversions of glucose-6-phosphate in the liver.

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles (liver)

- The liver plays an important regulatory role in metabolism by buffering the level of blood glucose.
- Two enzymes for glucose phosphorylation: hexokinase and glucokinase (type-IV hexokinase). Unlike hexokinase, glucokinase has a low affinity for glucose. Its *Km* for glucose is high, on the order of 10 m*M*. When blood glucose levels are high, glucokinase activity augments hexokinase in phosphorylating glucose as an initial step leading to its storage in glycogen.
- The major metabolic hormones—epinephrine, glucagon, and insulin—all influence glucose metabolism in the liver to keep blood glucose levels relatively constant.
- The liver is a major center for fatty acid turnover. When the demand for metabolic energy is high, triacylglycerols are broken down and fatty acids are degraded in the liver to acetyl-CoA to form ketone bodies, which are exported to the heart, brain, and other tissues. If energy demands are low, fatty acids are incorporated into triacylglycerols that are carried to adipose tissue for deposition as fat.

How Is Metabolism Integrated in a Multicellular Organism?

The Major Organ Systems Have Specialized Metabolic Roles **(liver)**

- Cholesterol is also synthesized in the liver from two-carbon units derived from acetyl-CoA.
- In addition to these central functions in carbohydrate and fat-based energy metabolism, the liver serves other purposes. For example, the liver can use amino acids as metabolic fuels. Amino acids are first converted to their corresponding *α*-keto acids by aminotransferases. The amino group is excreted after incorporation into urea in the urea cycle. The carbon skeletons of glucogenic amino acids can be used for glucose synthesis, whereas those of ketogenic amino acids appear in ketone bodies.
- The liver is also the principal detoxification organ in the body. The endoplasmic reticulum of liver cells is rich in enzymes that convert biologically active substances such as hormones, poisons, and drugs into less harmful byproducts.
- **Liver disease** leads to serious metabolic derangements, particularly in amino acid metabolism. In cirrhosis, the liver becomes defective in converting $NH4^+$ to urea for excretion, and blood levels of $NH4^+$ rise. Ammonia is toxic to the central nervous system, and coma ensues.

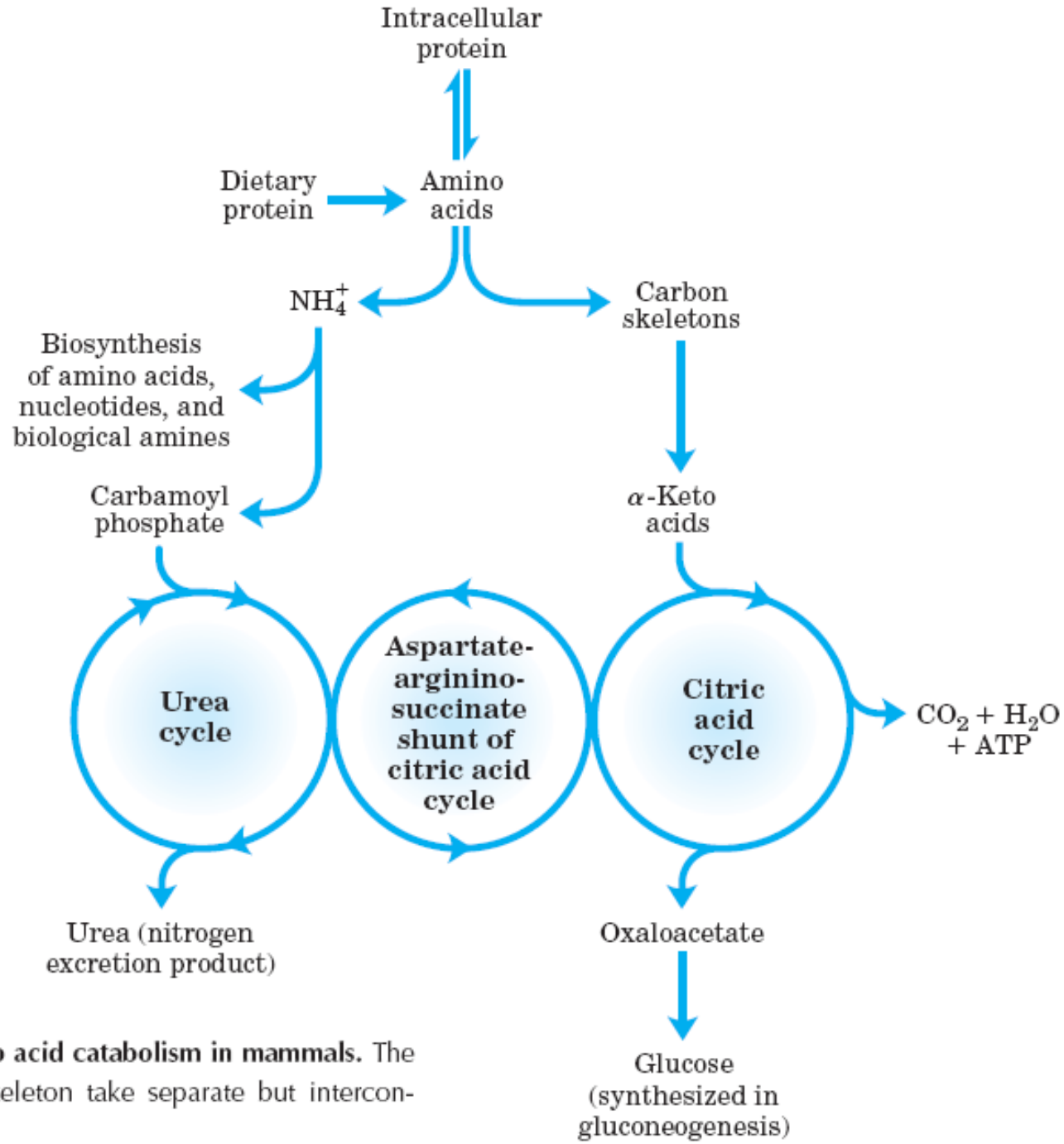


FIGURE 18–1 Overview of amino acid catabolism in mammals. The amino groups and the carbon skeleton take separate but interconnected pathways.

Ammonia Is Toxic to Animals. Why????