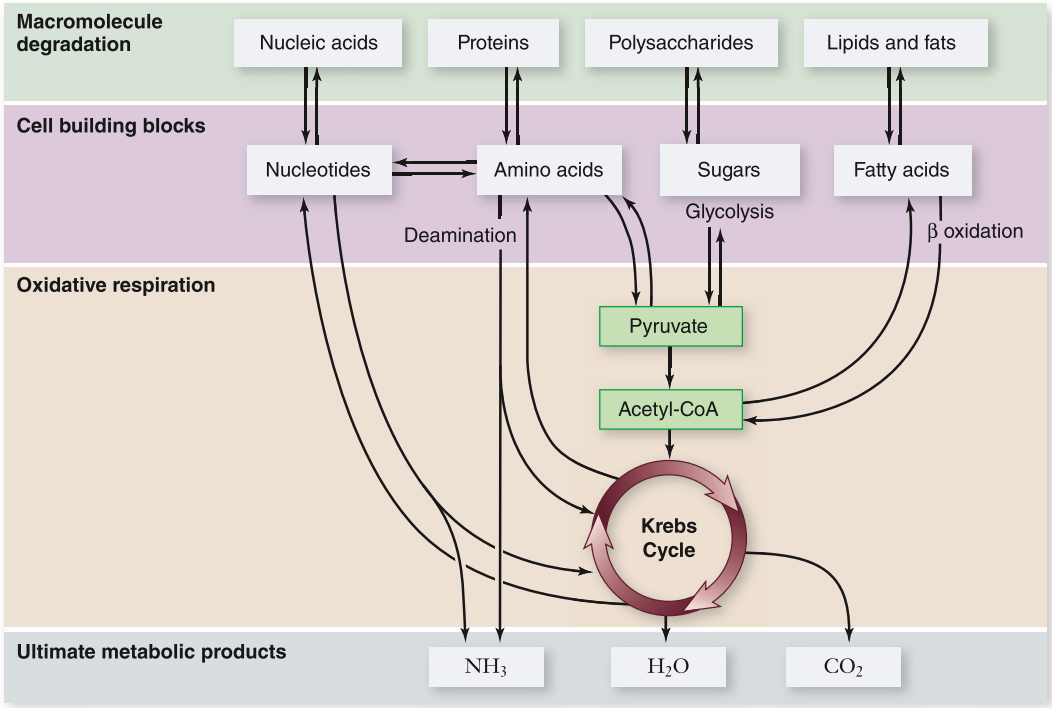


Figure 7.20 How cells extract chemical energy. All eukaryotes and many prokaryotes extract energy from organic molecules by oxidizing them. The first stage of this process, breaking down macromolecules into their constituent parts, yields little energy. The second stage, oxidative or aerobic respiration, extracts energy, primarily in the form of high-energy electrons, and produces water and carbon dioxide. Key intermediates in these energy pathways are also used for biosynthetic pathways, shown by reverse arrows.

particularly proteins and fats, are also important sources of energy (figure 7.20).

Catabolism of proteins removes amino groups

Proteins are first broken down into their individual amino acids. The nitrogen-containing side group (the amino group) is then removed from each amino acid in a process called **deamination.** A series of reactions converts the carbon chain that remains into a molecule that enters glycolysis or the Krebs cycle. For example, alanine is converted into pyruvate, glutamate into α-ketoglutarate (figure 7.21), and aspartate into oxaloacetate. The reactions of glycolysis and the Krebs cycle then extract the high-energy electrons from these molecules and put them to work making ATP.

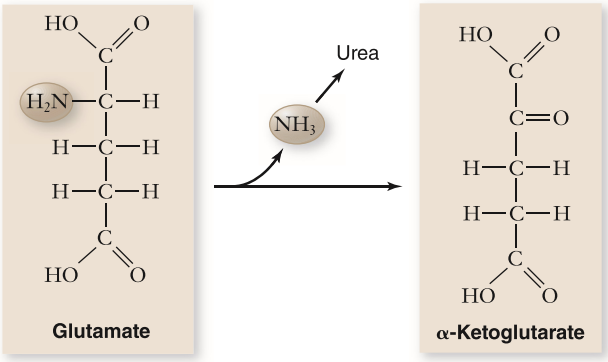


Figure 7.21 Deamination. After proteins are broken down into their amino acid constituents, the amino groups are removed from the amino acids to form molecules that participate in glycolysis and the Krebs cycle. For example, the amino acid glutamate becomes α-ketoglutarate, a Krebs cycle intermediate, when it loses its amino group.

Catabolism of fatty acids produces acetyl groups for the Krebs cycle

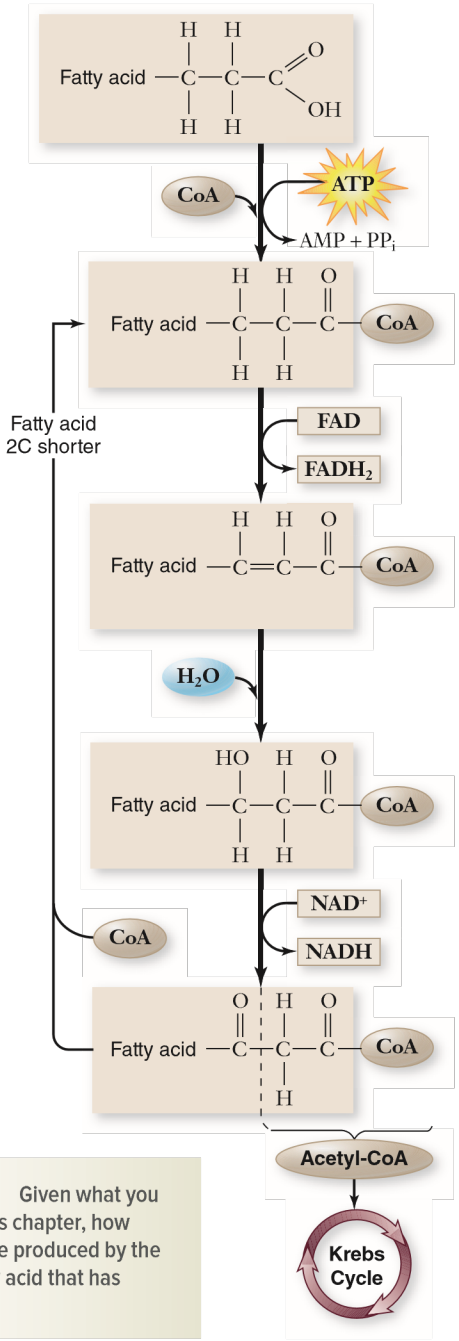
Fats are broken down into fatty acids plus glycerol. Long-chain fatty acids typically have an even number of carbons, and the many C—H bonds provide a rich harvest of energy. Fatty acids are oxidized in the matrix of the mitochondrion. Enzymes remove the 2-carbon acetyl groups from the end of each fatty acid until the entire fatty acid is converted into acetyl groups (figure 7.22). Each acetyl group is combined with coenzyme A to form acetyl-CoA. This process is known as **β oxidation.** This process is oxygen-dependent, which explains why aerobic exercise burns fat, but anaerobic exercise does not.

How much ATP does the catabolism of fatty acids produce? Let's compare a hypothetical 6-carbon fatty acid with the 6-carbon glucose molecule, which we've said yields about 30 molecules of ATP in a eukaryotic cell. Two rounds of β oxidation would convert the fatty acid into three molecules of acetyl-CoA. Each round requires one molecule of ATP to prime the process, but it also produces one molecule of NADH and one of $FADH_2$. These molecules together yield four molecules of ATP (assuming 2.5 ATP per NADH, and 1.5 ATP per $FADH_2$).

The oxidation of each acetyl-CoA in the Krebs cycle ultimately produces an additional 10 molecules of ATP. Overall, then, the ATP yield of a 6-carbon fatty acid is approximately: 8 (from two rounds of β oxidation) − 2 (for priming those two rounds) + 30 (from oxidizing the three acetyl-CoAs) = 36 molecules of ATP. Therefore, the respiration of a 6-carbon fatty acid yields 20% more ATP than the respiration of glucose.

Moreover, a fatty acid of that size would weigh less than two thirds as much as glucose, so a gram of fatty acid contains more than twice as many kilocalories as a gram of glucose. You can see from this fact why fat is a storage molecule for excess energy in

Figure 7.22
β oxidation.
Through a series of reactions known as β oxidation, the last two carbons in a fatty acid combine with coenzyme A to form acetyl-CoA, which enters the Krebs cycle. The fatty acid, now two carbons shorter, enters the pathway again and keeps reentering until all its carbons have been used to form acetyl-CoA molecules. Each round of β oxidation uses one molecule of ATP and generates one molecule each of $FADH_2$ and NADH.



Data analysis Given what you have learned in this chapter, how many ATP would be produced by the oxidation of a fatty acid that has 16 carbons?

many types of animals. If excess energy were stored instead as carbohydrate, as it is in plants, animal bodies would have to be much bulkier.

A small number of key intermediates connect metabolic pathways

Oxidation pathways of food molecules are interrelated in that a small number of key intermediates, such as pyruvate and acetyl-CoA, link the breakdown from different starting points. These key intermediates allow the interconversion of different types of molecules, such as sugars and amino acids (see figure 7.20).

Cells can make glucose, amino acids, and fats, as well as getting them from external sources. They use reactions similar to those that break down these substances. In many cases, the reverse pathways even share enzymes if the free-energy changes are small. For example, gluconeogenesis, the process of making new glucose, uses all but three enzymes of the glycolytic pathway. Thus, much of glycolysis runs forward or backward, depending on the concentrations of the intermediates—with only three key steps having different enzymes for forward and reverse directions.

Acetyl-CoA has many roles

Many different metabolic processes generate acetyl-CoA. Not only does the oxidation of pyruvate produce it, but the metabolic breakdown of proteins, fats, and other lipids also generates acetyl-CoA. Indeed, almost all molecules catabolized for energy are converted into acetyl-CoA.

Acetyl-CoA has a role in anabolic metabolism as well. Units of two carbons derived from acetyl-CoA are used to build up the hydrocarbon chains in fatty acids. Acetyl-CoA produced from a variety of sources can therefore be channeled into fatty acid synthesis or into ATP production, depending on the organism's energy requirements. Which of these two options is taken depends on the level of ATP in the cell.

When ATP levels are high, the oxidative pathway is inhibited, and acetyl-CoA is channeled into fatty acid synthesis. This explains why many animals (humans included) develop fat reserves when they consume more food than their activities require. Alternatively, when ATP levels are low, the oxidative pathway is stimulated, and acetyl-CoA flows into energy-producing oxidative metabolism.

Learning Outcomes Review 7.9

Proteins can be broken into their constituent amino acids, which are then deaminated and can enter metabolism at glycolysis or different steps of the Krebs cycle. Fats can be broken into units of acetyl-CoA by β oxidation and then fed into the Krebs cycle. Many metabolic processes can be used reversibly, to either build up (anabolism) or break down (catabolism) the major biological macromolecules. Key intermediates, such as pyruvate and acetyl-CoA, connect these processes.

- *Can fats be oxidized in the absence of O_2?*

7.10 Evolution of Metabolism

Learning Outcome

1. *Describe one possible hypothesis for the evolution of metabolism.*

We talk about cellular respiration as a continuous series of stages, but it is important to note that these stages evolved over time, and metabolism has changed a great deal in that time. Both anabolic

processes and catabolic processes evolved in concert with each other. We do not know the details of this biochemical evolution, or the order of appearance of these processes. Therefore the following timeline is based on the available geochemical evidence and represents a hypothesis rather than a strict timeline.

The earliest life-forms degraded carbon-based molecules present in the environment

The most primitive forms of life are thought to have obtained chemical energy by degrading, or breaking down, organic molecules that were abiotically produced—that is, carbon-containing molecules formed by inorganic processes on the early Earth.

The first major event in the evolution of metabolism was the origin of the ability to harness chemical bond energy. At an early stage, organisms began to store this energy in the bonds of ATP.

The evolution of glycolysis also occurred early

The second major event in the evolution of metabolism was glycolysis, the initial breakdown of glucose. As proteins evolved diverse catalytic functions, it became possible to capture a larger fraction of the chemical bond energy in organic molecules by breaking chemical bonds in a series of steps.

Glycolysis undoubtedly evolved early in the history of life on Earth, because this biochemical pathway has been retained by all living organisms. It is a chemical process that does not appear to have changed for more than 2 billion years.

Anoxygenic photosynthesis allowed the capture of light energy

The third major event in the evolution of metabolism was anoxygenic photosynthesis. Early in the history of life, a different way of generating ATP evolved in some organisms. Instead of obtaining energy for ATP synthesis by reshuffling chemical bonds, as in glycolysis, these organisms developed the ability to use light to pump protons out of their cells and to use the resulting proton gradient to power the production of ATP through chemiosmosis.

Photosynthesis evolved in the absence of oxygen and works well without it. Dissolved H_2S, present in the oceans of the early Earth beneath an atmosphere free of oxygen gas, served as a ready source of hydrogen atoms for building organic molecules. Free sulfur was produced as a by-product of this reaction.

Oxygen-forming photosynthesis used a different source of hydrogen

The substitution of H_2O for H_2S in photosynthesis was the fourth major event in the history of metabolism. Oxygen-forming photosynthesis employs H_2O rather than H_2S as a source of hydrogen atoms and their associated electrons. Because it garners its electrons from reduced oxygen rather than from reduced sulfur, it generates oxygen gas rather than free sulfur.

More than 2 BYA, small cells capable of carrying out this oxygen-forming photosynthesis, such as cyanobacteria, became the dominant forms of life on Earth. Oxygen gas began to accumulate in the atmosphere. This was the beginning of a great transition that changed conditions on Earth permanently. Our atmosphere is now 20.9% oxygen, every molecule of which is derived from an oxygen-forming photosynthetic reaction.

Nitrogen fixation provided new organic nitrogen

Nitrogen is available from dead organic matter, and from chemical reactions that generated the original organic molecules. For life to expand, a new source of nitrogen was needed. Nitrogen fixation was the fifth major step in the evolution of metabolism. Proteins and nucleic acids cannot be synthesized from the products of photosynthesis because both of these biologically critical molecules contain nitrogen. Obtaining nitrogen atoms from N_2 gas, a process called *nitrogen fixation,* requires breaking an $N \equiv N$ triple bond.

This important reaction evolved in the hydrogen-rich atmosphere of the early Earth, where no oxygen was present. Oxygen acts as a poison to nitrogen fixation, which today occurs only in oxygen-free environments or in oxygen-free compartments within certain prokaryotes.

Aerobic respiration utilized oxygen

Respiration is the sixth and final event in the history of metabolism. Aerobic respiration employs the same kind of proton pumps as photosynthesis and is thought to have evolved as a modification of the basic photosynthetic machinery.

Biologists think that the ability to carry out photosynthesis without H_2S first evolved among purple nonsulfur bacteria, which obtain their hydrogens from organic compounds instead. It was perhaps inevitable that among the descendants of these respiring photosynthetic bacteria, some would eventually do without photosynthesis entirely, subsisting only on the energy and electrons derived from the breakdown of organic molecules. The mitochondria within all eukaryotic cells are thought to be descendants of these bacteria.

The complex process of aerobic metabolism developed over geological time, as natural selection favored organisms with more efficient methods of obtaining energy from organic molecules. The process of photosynthesis, as you have seen in this concluding section, has also developed over time, and the rise of photosynthesis changed life on Earth forever. Chapter 8 explores photosynthesis in detail.

Learning Outcome Review 7.10

Major milestones in the evolution of metabolism include the evolution of pathways to extract energy from organic compounds, the pathways of photosynthesis, and those of nitrogen fixation. Photosynthesis began as an anoxygenic process that later evolved to produce free oxygen, thus allowing the evolution of aerobic metabolism.

- ***What evidence can you cite for this hypothesis of the evolution of metabolism?***

Chapter Review

7.1 Overview of Respiration (figure 7.5)

Cellular oxidations are usually also dehydrogenations.

Cellular respiration is the complete oxidation of glucose.

Aerobic respiration uses oxygen as the final electron acceptor for redox reactions. Anaerobic respiration utilizes inorganic molecules as acceptors, and fermentation uses organic molecules.

Electron carriers play a critical role in energy metabolism.

Electron carriers can be reversibly oxidized and reduced. For example, NAD^+ is reduced to NADH by acquiring two electrons; NADH supplies these electrons to other molecules to reduce them.

Respiration harvests energy in stages.

Mitochondria of eukaryotic cells move electrons in steps via the electron transport chain to capture energy efficiently.

ATP plays a central role in metabolism.

The ultimate goal of cellular respiration is synthesis of ATP, which is used to power most of the cell's activities.

Cells make ATP by two fundamentally different mechanisms.

Substrate-level phosphorylation transfers a phosphate directly to ADP (figure 7.4). Oxidative phosphorylation generates ATP via the enzyme ATP synthase, powered by a proton gradient.

7.2 Glycolysis: Splitting Glucose (figures 7.6 & 7.7)

Glycolysis converts glucose into two pyruvate, forming two ATP and two NADH in the process.

Priming reactions add two phosphates to glucose; this is cleaved into two 3-carbon molecules of glyceraldehyde 3-phosphate (G3P). Oxidation of G3P transfers electrons to NAD^+, yielding NADH. After four more reactions, the final product is two molecules of pyruvate. Glycolysis produces 2 net ATP, 2 NADH, and 2 pyruvate.

Glycolysis is an ancient process with a low energy yield, but it can be efficient with up to 40% of available energy trapped as ATP. Glycolysis was probably the first catabolic reaction to evolve.

NADH must be recycled to continue respiration.

In the presence of oxygen, pyruvate is oxidized to acetyl-CoA, which can be oxidized by the Krebs cycle. This process leads to a large amount of ATP. In the absence of oxygen, a fermentation reaction uses all or part of pyruvate to oxidize NADH.

In the presence of oxygen, NADH passes electrons to the electron transport chain. In the absence of oxygen, NADH passes the electrons to an organic molecule such as acetaldehyde (fermentation).

7.3 The Oxidation of Pyruvate Produces Acetyl-CoA (figure 7.9)

Pyruvate is oxidized to yield 1 CO_2, 1 NADH, and 1 acetyl-CoA. Acetyl-CoA enters the Krebs cycle as 2-carbon acetyl units.

7.4 The Krebs Cycle (figures 7.10 & 7.11)

An overview of the Krebs cycle.

The Krebs cycle extracts electrons and synthesizes one ATP.

The first reaction is an irreversible condensation that produces citrate; it is inhibited when ATP is plentiful. The second and third reactions rearrange citrate to isocitrate. The fourth and fifth reactions are oxidations; in each reaction, one NAD^+ is reduced to NADH. The sixth reaction is a substrate-level phosphorylation producing GTP, and from that ATP. The seventh reaction is another oxidation that reduces FAD to $FADH_2$. Reactions eight and nine regenerate oxaloacetate, including one final oxidation that reduces NAD^+ to NADH.

Glucose becomes CO_2 and potential energy.

As a glucose molecule is broken down to CO_2, some of its energy is preserved in 4 ATP, 10 NADH, and 2 $FADH_2$.

Following the electrons in the reactions reveals the direction of transfer.

7.5 The Electron Transport Chain and Chemiosmosis (figure 7.12)

The electron transport chain produces a proton gradient.

In the inner mitochondrial membrane, NADH is oxidized to NAD^+ by NADH dehydrogenase. Electrons move through ubiquinone and the bc_1 complex to cytochrome oxidase, where they join with H^+ and O_2 to form H_2O. This results in three protons being pumped into the intermembrane space. For $FADH_2$, electrons are passed directly to ubiquinone. Thus only two protons are pumped into the intermembrane space.

Electron transport powers proton pumps in the inner membrane.

Chemiosmosis utilizes the electrochemical gradient to produce ATP.

ATP synthase is a molecular rotary motor.

Protons diffuse back into the mitochondrial matrix via the ATP synthase channel. The enzyme uses this energy to synthesize ATP (figure 7.15).

7.6 Energy Yield of Aerobic Respiration

The theoretical yield for eukaryotes is 30 molecules of ATP per glucose molecule (figure 7.16).

Calculation of P/O ratios has changed over time.

7.7 Regulation of Aerobic Respiration

Glucose catabolism is controlled by the concentration of ATP molecules and intermediates in the Krebs cycle (figure 7.17).

7.8 Oxidation Without O_2

In the absence of oxygen other final electron acceptors can be used for respiration.

Methanogens use carbon dioxide.

Sulfur bacteria use sulfate.

Fermentation uses organic compounds as electron acceptors (figure 7.19).

Fermentation is the regeneration of NAD^+ by oxidation of NADH and reduction of an organic molecule. In yeast, pyruvate is decarboxylated, then reduced to ethanol. In animals, pyruvate is reduced directly to lactate.

7.9 Catabolism of Proteins and Fats

Catabolism of proteins removes amino groups (figure 7.21).

Catabolism of fatty acids produces acetyl groups for the Krebs cycle.

Fatty acids are converted to acetyl groups by successive rounds of β oxidation (figure 7.22). These acetyl groups feed into the Krebs cycle to be oxidized and generate NADH for electron transport.

A small number of key intermediates connect metabolic pathways.

Acetyl-CoA has many roles.
With high ATP, acetyl-CoA is converted into fatty acids.

7.10 Evolution of Metabolism

Major milestones are recognized in the evolution of metabolism; the order of events is hypothetical.

The earliest life-forms degraded carbon-based molecules present in the environment.

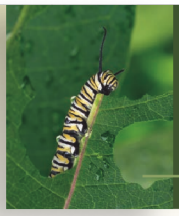
The evolution of glycolysis also occurred early.

Anoxygenic photosynthesis allowed the capture of light energy.

Oxygen-forming photosynthesis used a different source of hydrogen.

Nitrogen fixation provided new organic nitrogen.

Aerobic respiration utilized oxygen.



Review Questions

UNDERSTAND

1. An *autotroph* is an organism that
   a. extracts energy from organic sources.
   b. converts energy from sunlight into chemical energy.
   c. relies on the energy produced by other organisms as an energy source.
   d. does both a and b.
2. Which of the following processes is (are) required for the complete oxidation of glucose?
   a. The Krebs cycle
   b. Glycolysis
   c. Pyruvate oxidation
   d. All of the choices are correct.
3. Which of the following is NOT a product of glycolysis?
   a. ATP
   b. Pyruvate
   c. CO_2
   d. NADH
4. Glycolysis produces ATP by
   a. phosphorylating organic molecules in the priming reactions.
   b. the production of glyceraldehyde 3-phosphate.
   c. substrate-level phosphorylation.
   d. the reduction of NAD^+ to NADH.
5. What is the role of NAD^+ in the process of cellular respiration?
   a. It functions as an electron carrier.
   b. It functions as an enzyme.
   c. It is the final electron acceptor for anaerobic respiration.
   d. It is a nucleotide source for the synthesis of ATP.
6. The reactions of the Krebs cycle occur in the
   a. inner membrane of the mitochondria.
   b. intermembrane space of the mitochondria.
   c. cytoplasm.
   d. matrix of the mitochondria.
7. The electrons carried by NADH and $FADH_2$ can be
   a. pumped into the intermembrane space.
   b. transferred to the ATP synthase.
   c. moved between proteins in the inner membrane of the mitochondrion.
   d. transported into the matrix of the mitochondrion.

APPLY

1. Which of the following is NOT a true statement regarding cellular respiration?
   a. Enzymes catalyze reactions that transfer electrons.
   b. Electrons have a higher potential energy at the end of the process.
   c. Carbon dioxide gas is a by-product.
   d. The process involves multiple redox reactions.
2. The direct source of energy for the ATP produced by ATP synthase comes from
   a. the electron transport chain.
   b. a proton gradient.
   c. substrate-level phosphorylation.
   d. the oxidation reactions occurring during respiration.
3. Anaerobic respiration
   a. occurs in humans in the absence of O_2.
   b. occurs in yeast and is how we make beer and wine.
   c. yields less energy than aerobic respiration because other final electron acceptors have lower affinity for electrons than O_2.
   d. yields more energy than aerobic respiration because other final electron acceptors have higher affinity for electrons than O_2.
4. What is the importance of fermentation to cellular metabolism?
   a. It generates glucose for the cell in the absence of O_2.
   b. It oxidizes NADH to NAD^+ during electron transport.
   c. It oxidizes NADH to NAD^+ in the absence of O_2.
   d. It reduces NADH to NAD^+ in the absence of O_2.
5. The link between electron transport and ATP synthesis
   a. is a high-energy intermediate like phosphoenol pyruvate.
   b. is the transfer of electrons to ATP synthase.
   c. is a proton gradient.
   d. depends on the absence of oxygen.
6. A chemical agent that makes holes in the inner membrane of the mitochondria would
   a. stop the movement of electrons down the electron transport chain.
   b. stop ATP synthesis.
   c. stop the Krebs cycle.
   d. All of the choices are correct.

7. Yeast cells that have mutations in genes that encode enzymes in glycolysis can still grow on glycerol. They are able to utilize glycerol because it
   a. enters glycolysis after the step affected by the mutation.
   b. can feed into the Krebs cycle and generate ATP via electron transport and chemiosmosis.
   c. can be utilized by fermentation.
   d. can donate electrons directly to the electron transport chain.

SYNTHESIZE

1. Use the following table to outline the relationship between the molecules and the metabolic reactions.

Molecules	Glycolysis	Cellular Respiration
Glucose		
Pyruvate		
Oxygen		
ATP		
CO_2		

2. Human babies and hibernating or cold-adapted animals are able to maintain body temperature (a process called *thermogenesis*) due to the presence of brown fat. Brown fat is characterized by a high concentration of mitochondria. These brown fat mitochondria have a special protein located within their inner membranes. *Thermogenin* is a protein that functions as a passive proton transporter. Propose a likely explanation for the role of brown fat in thermogenesis based on your knowledge of metabolism, transport, and the structure and function of mitochondria.

3. Recent data indicate a link between colder temperatures and weight loss. If adults retain brown fat, how could this be explained?