The Brain on Ketones: Can It Be Good?

For some individuals with epilepsy, a high-fat, low-carbohydrate ketogenic diet can prevent or reduce seizures.
Energy Metabolism: The Interactions and Transformations of Living Cells

LEARNING OBJECTIVES

- Describe the function of enzymes and coenzymes in metabolism. (Infographic 15.1 and Infographic 15.2)
- Identify the primary energy currency of the cell and the site in the cell where that compound is mainly synthesized. (Infographic 15.3 and Infographic 15.4)
- Describe oxidation-reduction reactions and the role of coenzymes in these reactions. (Infographic 15.5 and Infographic 15.6)
- List the four major pathways involved in ATP production, and describe the one common outcome of all but the last pathway. (Infographic 15.6 and Infographic 15.12)
- Contrast the two phases of glycolysis. (Infographic 15.7)
- List the products and substrates of the citric acid cycle, and describe this cycle’s primary function. (Infographic 15.8)
- Explain how the electron transport chain is involved in the production of ATP. (Infographic 15.9)
- Explain when and why pyruvate is converted to lactate. (Infographic 15.10)
- Describe the process of beta-oxidation. (Infographic 15.11)
- Identify the functions of the vitamins, niacin, riboflavin, pantothenic acid, and vitamin B6 in energy metabolism. (Infographics 15.5, 15.7, 15.8, 15.11, and 15.14)
- Describe the metabolic conditions that promote ketone body synthesis. (Infographic 15.13)
- Identify the first step in the use of amino acids for energy or to synthesize glucose or fatty acids. (Infographic 15.13)
- Describe why the production of ketone bodies helps preserve body proteins during long-term fasting or with a low-carbohydrate diet. (Infographic 15.13 and Infographic 15.14)
- Identify the hormones that promote anabolic versus catabolic processes during feasting and fasting, respectively. (Infographic 15.15)
- Summarize the key metabolic changes that occur in adipose tissue, liver, muscle, and the brain as we shift from fasting to feasting. (Infographic 15.15)
In March 1993, Jim Abrahams was pushing his 11-month-old son Charlie in a swing when Charlie’s head suddenly twitched and his arm flew up in the air. Within days, these strange motions intensified, and every few days Charlie began having serious seizures in which he would drop to the ground and convulse.

Jim and his wife immediately sought medical help, first from Charlie’s pediatrician and then from the leading pediatric neurologist at the University of California, Los Angeles, close to where they lived. Jim, a Hollywood movie director, cowrote and directed the highly successful 1980 slapstick comedy *Airplane!* as well as other blockbuster movies.

Charlie, the Abrahams were told, had epilepsy, a neurological disorder characterized by recurrent seizures and abnormal electrical activity in the brain. Doctors immediately started Charlie on a powerful seizure-controlling drug, but it didn’t work. They then tried a second drug, but it didn’t work either. In fact, Charlie’s seizures worsened. The Abrahams sought opinions from other leading U.S. neurologists, but every physician told them that drugs and surgery were the only treatment options. One by one, the Abrahams tried the available medications, and when those drugs failed, Charlie had brain surgery. Still, his seizures didn’t abate.

Frustrated and desperate, Jim decided to research Charlie’s condition himself at a medical library. That’s when he came across a study by researchers at the Johns Hopkins University School of Medicine that had been reported in a leading epilepsy journal. The study suggested that a ketogenic diet—a low-carbohydrate, high-fat diet that causes the body to break down fat and convert it into molecules called *ketone bodies*—could treat epilepsy in children. When Jim mentioned the Johns Hopkins’ study to Charlie’s pediatric neurologist, the doctor was skeptical. Nevertheless, the Abrahams flew across the country to Johns Hopkins to meet with researchers there and to learn how to put Charlie on the ketogenic diet. Two days after starting the diet, Charlie’s seizures stopped.

Since 1993, research on the use of the ketogenic diet to treat epilepsy has exploded—in part because the Abrahams founded the nonprofit Charlie Foundation to fund additional research on the ketogenic diet treatment. Jim also wrote and directed a movie on the ketogenic diet as a treatment for epilepsy, which starred actor Meryl Streep.

Today the ketogenic diet—now better known as the “keto diet”—is extremely popular among health enthusiasts, although there are no compelling data that suggest it is beneficial for the general population. One of the most popular reasons for undertaking a ketogenic diet is for weight loss. A ketogenic diet restricts carbohydrate intake to 20–50 g per day, which necessitates an increase in total fat intake for the diet to provide adequate calories. For this reason, ketogenic diets are also referred to as low-carbohydrate, high-fat (LCHF) diets. There is no consistent or compelling evidence that a ketogenic diet is any more effective at inducing weight loss in the general population than any other diet that reduces energy intake. However, some evidence suggests that individuals with prediabetes or type 2 diabetes may initially lose weight slightly faster on a ketogenic diet compared to a fat-restricted diet. In these individuals, a ketogenic diet also typically results in at least short-term improvements...
in blood glucose control. However, the ketogenic diet has been shown to impair high-intensity exercise performance and may also pose health risks. For example, high-fat diets have been shown to impair cognitive function in healthy humans, and epidemiological studies have found that individuals who consume low-carbohydrate diets have an increased risk of dying from cardiovascular disease and cancer. Furthermore, the long-term safety or sustainability of ketogenic diets has not yet been demonstrated.

More than 3000 studies have now been published on the use of the ketogenic diet to treat epilepsy. The consensus is that the diet "is a powerful, proven medical treatment for epilepsy widely used all over the world," according to Eric Kossoff, MD, a pediatric neurologist at the Johns Hopkins School of Medicine who has conducted much of the research. Although scientists still aren’t certain exactly how the diet works to control seizures (and they assume many different biological mechanisms may be involved), the diet almost certainly helps because of its effects on the body's metabolism and chemical pathways to the brain.

Metabolism encompasses all the life-sustaining chemical reactions occurring in living organisms that transform one molecule into another one. (Recall that metabolism is introduced in Chapter 3.) The molecular transformation that occurs during metabolism is accomplished through reactions that may rearrange atoms within a molecule or add atoms to or remove them from a molecule. The vast majority of chemical reactions that occur in the body are catalyzed (initiated and accelerated) by enzymes, which are proteins that facilitate chemical reactions without themselves being altered. Because enzymes are not altered during the reaction, they can catalyze the same reaction over and over again. (INFOGRAPHIC 15.1)

The molecule on which an enzyme acts is referred to as a substrate, and the modified molecule that the reaction yields is called the product. Many enzymes require small, organic,

INFOGRAPHIC 15.1 How Do Enzymes Work?

Enzymes are proteins that facilitate chemical reactions without being altered themselves. This enzyme (amylase) breaks down starch, a long chain of sugar (glucose) molecules.

Starch binds to the enzyme. The enzyme breaks the bond between two glucose molecules. Two starch fragments are released. The enzyme can now act again on another starch molecule. To bind and initiate a reaction, the shape of this amylase enzyme must exactly match that of the starch molecule.

Why won't this enzyme break down lipids or proteins?
Small molecules called **coenzymes** to function. (INFOGRAPHIC 15.2) Coenzymes bind at a location on the enzyme known as the active site and form an active enzyme; only then is the enzyme capable of catalyzing its designated reaction. All of the B vitamins function as coenzymes, as do vitamin C and vitamin K (see Chapter 8 and Appendix 3). For example, **coenzyme A (CoA)** is synthesized from pantothenic acid (vitamin B₅), and **nicotinamide adenine dinucleotide (NAD⁺)** is synthesized from niacin (vitamin B₃).

Many of the chemical transformations that occur within cells require that multiple individual reactions be completed in a series. For this reason, cellular metabolism is typically organized into **metabolic pathways**. Each pathway transforms its original substrate into a final product or products through a sequence of linked reactions catalyzed by enzymes. At each step in the pathway, the product formed in one reaction becomes the substrate for the next reaction in the pathway, with this process continuing until the final product is formed. One proposed reason for the success of the ketogenic diet in treating epilepsy is that the diet affects metabolic pathways that help brain cells maintain energy equilibrium, preventing seizures.

Many metabolic processes fall into one of two broad categories: **anabolism** and **catabolism** (introduced in Chapter 12). Anabolism is the synthesis of large molecules from smaller ones, requiring an input of energy. Commonly occurring anabolic processes synthesize proteins from amino acids, glycogen from glucose, and triglycerides from sources of excess calories (such as glucose and amino acids). Cell division and growth are also anabolic processes.

Catabolism, by contrast, is the breakdown of large molecules into smaller molecules and is generally accompanied by the release of energy. Catabolic processes supply the fuels needed to drive anabolism; they can also provide the substrates needed for a number of anabolic processes. The balance between all anabolic and catabolic processes over the course of several days will determine if an individual’s weight will remain stable or whether he or she will experience a change in body weight. For example, if the total number of catabolic processes exceeds the total number of anabolic processes, an individual’s body weight will decrease, as adipose tissue and muscle mass are lost.

Have you ever felt like your energy level was low and you didn’t feel like tackling routine chores or participating in activities that you would normally enjoy? Perhaps you wondered if there was something wrong with your metabolism or if the fuels you needed to supply the energy for these activities were in low supply. In reality, neither your metabolism nor your supply of fuels was likely to blame. Whereas very high-intensity exercise places heavy demands on available fuels, routine daily chores and activities create no such
challenges because most cells in our body can adapt to using a variety of fuels, including fatty acids, glucose, amino acids, and ketone bodies, specific compounds that the liver produces from primarily fatty acids when carbohydrate intake is low. Ketone bodies were the fuels that Charlie Abrahams’ body relied on when he was on the ketogenic diet, because LCHF diets increase the production of ketone bodies in the liver and reduce blood glucose levels. Our bodies are really quite good at mobilizing fuels and delivering them where they are needed to sustain normal functions. In this chapter on energy metabolism, you will learn how the fuels that we obtain from food are stored and later used to extract the energy needed to support body functions.

To develop a clear understanding of energy metabolism, it is important to first understand the scientific concept of energy. Unfortunately, our common use of phrases such as “My energy level is low” and “I’m feeling energetic” can confuse us. Someone who is described as being “energetic” is readily envisioned as being active, lively, and animated. Although we can easily see these characteristics, they are difficult to measure or quantify. Furthermore, these characteristics are fundamentally about motivation and desire but do not generally pertain to our capacity to do work and meet the physical demands of daily living. In contrast, energy—referring to the scientific concept—cannot be seen, but it can be measured and quantified. In Chapter 1, you learned that a unit of food energy is a kilocalorie (kcal), which can be determined by measuring the temperature change in a specific volume of water. In fact, a generally well-accepted definition of energy is “the capacity to produce changes within a system.”

The use of energy in our bodies results in three fundamental types of changes: It allows us to create chemical bonds, it produces heat, and it allows us to move—move objects outside our bodies, move our bodies, and move structures and chemical substances within and between our cells. To liberate this energy so that we can use it, we must metabolize our available fuels. And as Charlie’s experience with epileptic seizures suggests, the types of fuels that we provide to our body—and the way our body metabolizes them—can also have downstream effects on other body parts and organs, including the brain.

Energy metabolism includes all the chemical reactions that are involved in storing fuels or breaking them down to provide the energy necessary to drive a variety of chemical reactions and other cellular processes (such as active transport and muscle contractions). This energy generally comes from one of two main fuel sources: glucose and fatty acids. The source that a body uses for fuel depends in part on the foods the person eats: If a person’s diet is low in carbohydrates, as was the case with Charlie’s keto diet, fat (a source of fatty acids) becomes the primary source of energy. If a person’s diet is high in carbohydrates but low in fat and protein, carbohydrates become the primary fuel source. Both glucose and fatty acids are rich in chemical energy, which is stored in the chemical bonds that hold molecules together. As fuels are slowly metabolized and broken down, energy is released as the bonds are broken through chemical reactions. Therefore, as our fuels are progressively broken down, the product of each chemical reaction contains less energy than the starting substrate because the product of the reaction contains fewer bonds.

The energy released when chemical bonds are broken is not in a form the body cells
ENERGY METABOLISM: THE INTERACTIONS AND TRANSFORMATIONS OF LIVING CELLS

Adenosine Triphosphate (ATP) is produced during energy metabolism. ATP has a high energy content and is often referred to as the energy currency of cells.

Glucose oxidation (glycolysis) is the only ATP-producing pathway that occurs in the cytosol. All other pathways involved in the production of ATP occur in mitochondria, which produce the majority of ATP in most cells. Mitochondria are organelles surrounded by a double-membrane system composed of inner and outer membranes. The space enclosed by the inner membrane is called the mitochondrial matrix. Most of the functions carried out by mitochondria occur in the matrix, and in this location, the oxygen we breathe is linked to the generation of ATP.

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As a phosphate is released from ATP what can be captured to do work?

Energy is released when the bond between the second and third phosphate of ATP is broken. A portion of the released energy can be captured to do work, such as fueling muscle contractions. ADP is then used to re-form ATP by the three energy systems.

ADENOSINE TRIPHOSPHATE (ATP)
- a molecule containing three phosphate groups that is crucial in transferring energy from metabolic fuels to energy-requiring processes in the body

CYTOSOL
- the cellular fluid enclosed by the cell membrane

MITOCHONDRIA
- cellular organelles consisting of inner and outer membranes, where the majority of ATP is produced

MITOCHONDRIAL MATRIX
- the mitochondrial compartment enclosed by the mitochondrial inner membrane

OXIDATION
- the loss of electrons

REDUCTION
- the gain of electrons

As a phosphate is released from ATP what can be captured to do work?

The reactions of energy metabolism occur primarily in two cellular compartments, the cytosol and the mitochondria. Recall that cells are surrounded by a cell membrane. Within the cell membrane is an aqueous fluid called the cytosol as well as a number of cellular organelles and other structures. The membrane-enclosed organelles (such as mitochondria, endoplasmic reticulum, and the nucleus) carry out a variety of specialized functions. The cytoplasm includes the cytosol and all the organelles except the nucleus. (INFOGRAPHIC 15.4)

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Oxidation-reduction reactions involve the transfer of electrons between compounds and play a vital role in energy metabolism and ATP production. Oxidation is the loss of electrons, and reduction is the gain of electrons. Electrons do not float around freely in solution. Instead, they are transferred from one substance to another so that as one substance loses an electron, another substance simultaneously gains that electron. The substance that loses an electron is oxidized, and the...
Overview of Energy Metabolism

**INFOGRAPHIC 15.4** Cells The smallest functional unit of living organisms is the cell. The cell membrane separates the interior of the cell (the cytoplasm) from the extracellular fluid. (In the figure, only a few of the cellular organelles are labeled.) Mitochondria are where we extract the majority of energy from fuels to produce ATP.

The main pathways involved in capturing some of the energy present in chemical bounds to synthesize ATP are glycolysis, β-oxidation, the citric acid cycle, and the electron transport chain. Among these pathways, glycolysis (which begins the oxidation of glucose) is unique, because it is the only energy-yielding pathway found in the cytosol; the other three pathways all occur in the mitochondrial matrix.

Whereas glycolysis is the first stage of glucose oxidation, β-oxidation (β-oxidation) is the first step in the oxidation of fatty acids. As fuel metabolism proceeds, the intermediate compounds formed from the oxidation of our fuels enter the citric acid cycle, where their oxidation is completed. At the start of the citric acid cycle, the breakdown products from both glucose and fatty acids enter it as the 2-carbon molecule acetyl-CoA. In contrast, the carbon chains (or “carbon skeletons”) that remain following the initial metabolism of amino acids typically enter the citric acid cycle at one of several possible points. As these intermediate compounds generated by

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**FLAVIN ADENINE DINUCLEOTIDE (FAD)**
a coenzyme synthesized from the vitamin riboflavin that participates in oxidation-reduction reactions

**GLYCOLYSIS**
the breakdown of glucose in the cytosol

**BETA-OXIDATION (β-OXIDATION)**
the breakdown of fatty acids to 2-carbon molecules in the mitochondria

**CITRIC ACID CYCLE**
oddative pathway in the mitochondria that completes the oxidation of metabolic fuels and produces NADH and FADH₂.
Oxidation-reduction reactions involve the transfer of electrons (or hydrogen atoms) between compounds and are vital for the extraction and use of the energy that is supplied by the fuels that are provided in the foods we eat.

Because free electrons are not stable, their removal (oxidation) from one substance must be accompanied by their acceptance (reduction) by another substance.

Coenzymes NAD⁺ and FAD synthesized from the vitamins niacin and riboflavin, respectively, are often involved in transferring hydrogen atoms and/or electrons from one substance to another.

What are the two co-enzymes that are often required for oxidation-reduction reactions?
the initial oxidation of our fuels move through the citric acid cycle, their oxidation is completed and the reduced coenzymes NADH and FADH₂ are produced. (INFOGRAPHIC 15.6)

The reduced coenzymes generated in these pathways shuttle their high-energy electron cargo to the electron transport chain (ETC) in mitochondria, where a series of electron-carrier molecules are embedded in the inner mitochondrial membrane. As electrons are passed from one molecule to another, energy is released. This energy can be used to synthesize ATP.

**THE BREAKDOWN OF GLUCOSE**

**Glucose Metabolism Begins in the Cytosol and Is Completed in Mitochondria**

All cells in the body are able to utilize glucose as a fuel to produce ATP. (INFOGRAPHIC 15.7) The brain always requires that a significant
INFOGRAPHIC 15.7  Glycolysis is the metabolic pathway by which all cells can produce ATP by breaking down glucose to pyruvate. Glycolysis occurs in the cytosol of the cell and does not require oxygen.

Phase 1: Energy Investment
The first phase of glycolysis requires an input of energy from ATP.

1. Enzymes add two phosphate molecules from ATP to glucose, and rearrange the structure of glucose to form fructose.

2. The phosphorylated sugar (now fructose) is then cleaved into two, 3-carbon molecules, each with one phosphate.

3. Enzymes add a phosphate to each of these 3-carbon molecules. This does not use ATP.

4. These 3-carbon molecules are then oxidized, while two coenzymes NAD⁺ are reduced.

5. When O₂ availability is sufficient, the reduced coenzymes transfer the hydrogen atoms with their high-energy electrons into mitochondria.

6. In two separate enzymatic reactions, all four phosphates are transferred to ADP to form four molecules of ATP.

Phase 2: Energy Payoff
The second phase of glycolysis results in the net production of ATP.

How many ATP are gained for every molecule of glucose that is converted to pyruvate?
The Breakdown of Glucose

The amount of its energy be provided by glucose, and red blood cells obtain 100% of their energy from glucose because they lack mitochondria. Therefore, a source of glucose is essential for life. Glucose metabolism begins in the cytosol with glycolysis (or the glycolytic pathway), which is a non-oxygen-dependent process (and, therefore, is often referred to as being anaerobic). Glycolysis is a universal process that allows every cell in the body to extract energy from carbohydrates. The term glycolysis means "to break apart glucose." In general, glycolysis splits a 6-carbon glucose molecule into two 3-carbon molecules of pyruvate, with a net gain of two ATP molecules and the production of two reduced coenzymes.

More specifically, glycolysis is a multistep process that occurs in two phases: an energy investment phase and an energy payoff phase. During the energy investment phase, glucose undergoes phosphorylation, the addition of a phosphate molecule to a compound. Glucose is phosphorylated and rearranged into fructose, and then the fructose itself is phosphorylated. The energy invested through the addition of phosphates from two ATP molecules to fructose makes fructose more reactive than glucose. The doubly phosphorylated fructose then splits into two 3-carbon phosphate-containing molecules.

In the energy payoff phase of glycolysis, energy is harvested as the phosphorylated 3-carbon molecules are oxidized to form two molecules of pyruvate. During this phase of glycolysis, four ATP are produced. Since two ATP were used during the energy investment phase, there is a net yield of two ATP.

In addition, in the energy payoff phase, two NAD⁺ are reduced to NADH as the NAD⁺ acquire high-energy electrons. These high-energy electrons will then be transferred to the ETC in mitochondria so long as their rate of production does not exceed the capacity of the ETC.

Mitochondria are also where glucose oxidation is completed, and where ATP is produced in an aerobic (oxygen-dependent) manner. Pyruvate is transported from the cytosol into mitochondria, where the aerobic breakdown of pyruvate to carbon dioxide (CO₂) and water completes the oxidation of glucose.

The Bridge Reaction Prepares Pyruvate for Complete Oxidation

The fate of the two molecules of pyruvate produced from each molecule of glucose in glycolysis is largely determined by how quickly pyruvate is being produced. As long as the production rate of pyruvate does not exceed the capacity of mitochondria to utilize it, pyruvate will enter the mitochondria, where its oxidation can be completed. The aerobic oxidation of pyruvate is responsible for generating the majority of ATP derived from glucose metabolism. However, for pyruvate to enter the next major pathway of energy metabolism (the citric acid cycle), it must first be converted into the 2-carbon molecule acetyl-CoA, which requires the involvement of several vitamin-derived coenzymes, including NAD⁺ and coenzyme A. The production of acetyl-CoA is shown in step 1 in INFOGRAPHIC 15.8.

The Citric Acid Cycle Is the Final Step in Glucose Oxidation

The final step in the oxidation of glucose involves entry of acetyl-CoA into the citric acid cycle in the mitochondria (step 2). This pathway is also commonly referred to as the tricarboxylic acid (TCA) cycle and the Krebs cycle (after the scientist who first described it). The citric acid cycle is typically represented as a circle because the product (oxaloacetate) of the last reaction in the cycle is also a substrate in the first reaction that was used to generate oxaloacetate in the cycle.

Much like a busy traffic circle, the citric acid cycle is a major intersection in cellular metabolism, with reactants entering and intermediate products being removed at various points in the cycle.
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The citric acid cycle’s main role in ATP production is to oxidize acetyl-CoA by a series of oxidation-reduction reactions. As high-energy electrons are transferred from acetyl-CoA by these oxidation-reduction reactions, the reduced coenzymes NADH and FADH₂ are formed. In the process, two carbon atoms leave the cycle as CO₂. Although the cycle is referred
to as aerobic, oxygen is not directly required anywhere in the pathway. Instead, the requirement for oxygen is indirect: It is needed by the ETC to reoxidize NADH and FADH$_2$ back to NAD$^+$ and FAD so that those coenzymes can continue to participate in the citric acid cycle (see more about this in the next section).

In the citric acid cycle, the 2-carbon acetyl group of acetyl-CoA is joined to the 4-carbon molecule oxaloacetate to form the 6-carbon molecule citric acid (citrate). Citrate is oxidized as it moves through the cycle to produce two molecules of CO$_2$, four reduced coenzymes (three NADH and one FADH$_2$), and a guanosine triphosphate (GTP), which is similar to ATP.

**INFOGRAPHIC 15.9** **The Electron Transport Chain and Oxidative Phosphorylation**

Oxidative phosphorylation is the process by which ATP is formed by the flow of electrons from NADH and FADH$_2$ through the electron transport chain to oxygen.

1. NADH and FADH$_2$ produced during glycolysis, the citric acid cycle, and ß-oxidation are reoxidized to NAD$^+$ and FAD as they transfer their high-energy electrons to a series of electron carriers in the electron transport chain.

2. As electrons are transferred from one carrier to another, some of the released energy is used to pump protons across the inner mitochondrial membrane into the intermembrane space.

3. At the end of the electron transport chain, oxygen combines with two electrons and two protons (H$^+$) to produce water.

4. Some of the energy released from the electrons is conserved by the accumulation of protons in the intermembrane space. This energy can then be used to synthesize ATP.

5. ATP is synthesized as protons flow back into the mitochondrial matrix through the enzyme complex ATP synthase.

**Reduced Coenzymes Transfer High-Energy Electrons to the Electron Transport Chain**

With the completion of glucose oxidation in the citric acid cycle, the majority of the chemical bond energy originally present is now conserved in the high-energy electrons carried by coenzymes that were reduced in glycolysis, with the conversion of pyruvate to acetyl-CoA and with the oxidation of acetyl-CoA in the citric acid cycle. To use the energy conserved in reduced coenzymes, the reduced coenzymes transfer their high-energy electrons to the ETC embedded in the inner mitochondrial membrane.

As electrons move down the ETC, the requirement for oxygen is indirect: It is needed by the ETC to reoxidize NADH and FADH$_2$ back to NAD$^+$ and FAD so that those coenzymes can continue to participate in the citric acid cycle (see more about this in the next section).

What is the direct source of energy that is used to produce ATP?
The release of water from a reservoir behind a hydroelectric dam to produce electricity is similar to the accumulation of protons in the mitochondrial intermembrane space used to supply the energy for ATP synthesis.

The transfer of electrons from reduced coenzymes to the ETC is also critically important because it returns the coenzymes to their oxidized form, which allows them to continue participating in the oxidation of metabolic fuels. If the electron transfer did not occur, reduced coenzymes would accumulate and oxidized coenzymes would become depleted. With an inadequate number of coenzymes available to accept electrons from fuels as they are oxidized, oxidation would slow dramatically and eventually stop.

**Total Net Yield of ATP from Glucose Oxidation**

The complete aerobic oxidation of one molecule of glucose produces a total of 32 molecules of ATP from three different sources. Glycolysis produces a net yield of two ATP. Two ATP (GTP) are produced by the citric acid cycle, and 28 ATP are produced from the energy captured by the transport of electrons down the ETC. Because both the citric acid cycle and the ETC are aerobic pathways, 30 of the maximum 32 ATP molecules generated by glucose oxidation are produced in an oxygen-dependent manner.

**Under Some Conditions Pyruvate Is Converted to Lactate**

Glycolysis is often labeled as either aerobic or anaerobic, but in reality, there is only one glycolysis pathway. Also, the term anaerobic refers to conditions where oxygen is not present, which of course cannot occur in any normal living human tissue or cell, so this terminology can cause confusion. We can gain insight into the origin of these terms if we recall that the typical fate of pyruvate is to enter mitochondria and be converted to acetyl-CoA and then enter the citric acid cycle to be oxidized; these processes are indeed aerobic (dependent on adequate oxygen). In contrast, if oxygen is truly absent, pyruvate must be converted to lactate to allow glycolysis to continue (for reasons we will discuss shortly); however, this condition—an absence of oxygen—rarely, if ever, occurs under normal conditions (in humans). Nonetheless, the term anaerobic glycolysis has come to be applied to any circumstance where pyruvate is converted into lactate. (INFOGRAPHIC 15.10)
The Breakdown of Glucose

**INFOGRAPHIC 15.10 Aerobic versus Anaerobic Glycolysis** In aerobic glycolysis, reduced coenzymes are oxidized by the electron transport chain, whereas in anaerobic glycolysis, reduced coenzymes are oxidized by converting pyruvate to lactate.

**AEROBIC GLYCOLYSIS**

1. During glycolysis, two coenzymes are reduced when they each pick up a hydrogen atom (a hydrogen ion and an electron) as glucose is metabolized to pyruvate.

2. Typically, the reduced coenzymes (NADH) would be oxidized in the mitochondria as they deliver the hydrogen atom into mitochondria, with the electron entering the electron transport chain (ETC).

3. The transfer of electrons to the ETC regenerates the oxidized form of the coenzyme (NAD⁰⁺) that is needed for glycolysis to continue.

**ANAEROBIC GLYCOLYSIS**

4. Under some conditions, such as during intense exercise, or when oxygen availability is limited, glycolysis produces reduced coenzymes (NADH) faster than they can be oxidized by the ETC in mitochondria.

5. The limited capacity of the ETC to oxidize a sufficient number of reduced coenzymes (carrying a hydrogen atom) would cause glycolysis to slow dramatically as the availability of oxidized coenzymes (without a hydrogen atom) decreases.

6. To prevent glycolysis from slowing down, the reduced coenzymes can donate their hydrogen atom to pyruvate to form lactate.

7. The reduction of pyruvate to lactate quickly regenerates oxidized coenzymes, allowing glycolysis to continue at a rapid rate. This is referred to as “anaerobic” glycolysis even though it often occurs in situations where oxygen is abundant.

What are two ways that the coenzymes reduced during glycolysis can be returned to their oxidized form?

When rates of glycolysis are very high, how are the vast majority of coenzymes returned to their oxidized form?

How would the elimination of mitochondria from skeletal muscle affect both the availability of oxygen in muscle and its reliance on anaerobic glycolysis for ATP production?

Under some circumstances, glycolysis produces pyruvate (Chapter 12) and reduced coenzymes faster than the aerobic pathways in mitochondria can process them. This process occurs to meet the high energy demands of intense exercise: Glycolysis can operate so rapidly that it produces ATP faster than aerobic pathways even though only a small fraction of the available energy in glucose has been extracted. The high energy demand for rapid cell division is also believed to be the reason why many cancer cells produce large...
Cori cycle, in which the liver uses lactate to synthesize glucose (in a pathway called gluconeogenesis) and then returns the glucose to working muscles, where it is used to fuel contractions.

**FATTY ACID OXIDATION OCCURS IN THE MITOCHONDRIAL MATRIX**

Unlike glucose, the oxidation of fatty acids for energy occurs completely in mitochondria and only in aerobic conditions. Before fatty acids can be transported into the matrix, they must be activated by the enzymatic attachment of coenzyme A—a reaction that requires energy input equivalent to that of converting two molecules of ATP to ADP.

Once activated, fatty acids are transported into the mitochondrial matrix, they are oxidized by a process called beta-oxidation (β-oxidation). Similar to what occurred with the mitochondrial oxidation of pyruvate, β-oxidation involves the attachment of coenzyme A and the cutting off of two carbons at a time (as acetyl-CoA) from the fatty acid. However, with the release of each acetyl-CoA molecule from the fatty acid, two coenzymes (one NAD+ and one FAD) are reduced instead of just NAD+, as occurred with pyruvate.

For an 18-carbon fatty acid, beta-oxidation produces nine acetyl-CoA molecules that will be oxidized by the citric acid cycle. Because one coenzyme A was attached to the fatty acid when it was activated and the last reaction of β-oxidation yields two acetyl-CoA molecules, an 18-carbon fatty acid requires eight rounds of β-oxidation, producing 16 reduced coenzymes.

To summarize, the complete oxidation of an 18-carbon fatty acid by beta-oxidation and the citric acid cycle produces 52 reduced coenzymes, yielding 113 ATP as their high-energy electrons are transferred to the ETC. Each turn of the citric acid cycle produces the equivalent of one ATP (a GDP), so the oxidation of the 9 acetyl-CoA molecules yields 9 ATP, giving a total of 122 ATP produced. After subtracting the 2 ATP required for the initial activation of the fatty acid, the final net yield of ATP produced from an 18-carbon fatty acid is...
have untreated type 1 diabetes, a class of compounds called ketone bodies are synthesized from acetyl-CoA produced by β-oxidation in liver mitochondria. These compounds are β-hydroxybutyrate, acetoacetate, and acetone. Ketone bodies are produced when insulin concentrations are very low and the rate of fatty acid oxidation produces 120 ATP. INFOGRAPHIC 15.12 provides an overview of the use of glucose and fatty acids in cellular respiration, which is the production of ATP by the complete oxidation of metabolic fuels.

**Ketogenesis**

When individuals undergo fasting, follow a very low-carbohydrate diet, or

INFOGRAPHIC 15.11  **β-Oxidation** (beta-oxidation) is the process by which fatty acids are broken down in the mitochondria to 2-carbon acetyl-CoA molecules.
Cellular Respiration is the process by which the energy stored in fuels is transferred to ATP through a series of enzyme-catalyzed reactions. Aerobic respiration requires oxygen and occurs in mitochondria, where fatty acids and pyruvate are broken down to carbon dioxide and water.

1. Glycolysis occurs in the cytosol where glucose is broken down to two molecules of pyruvate, which produces two ATP and transfers four electrons to coenzymes.

2. Pyruvate is transported into mitochondria.

3. Both pyruvate and fatty acids are broken down to acetyl-CoA in mitochondria, releasing two electrons for pyruvate and four electrons for every acetyl-CoA released during the breakdown of fatty acids.

4. The 2-carbon “acetyl” portion of acetyl-CoA reacts with a 4-carbon molecule that is part of the citric acid cycle, forming the 6-carbon molecule citric acid, which gives the cycle its name. Coenzyme A is released in the process.

5. Through a series of reactions, the citric acid cycle removes two carbons from citric acid to produce two molecules of carbon dioxide and one ATP and transfers eight electrons to coenzymes.

6. Coenzymes transfer high-energy electrons to the electron transport chain (ETC).

7. As electrons move down the ETC, they lose energy, which is captured, and then used to synthesize the vast majority of the ATP that is produced during cellular respiration.

8. At the end of the ETC, electrons combine with oxygen and hydrogen to produce water.

What carries electrons produced during glycolysis, the citric acid cycle, and fatty acid oxidation to the electron transport chain?
Ketogenesis

INFOGRAPHIC 15.13 Ketone Body Synthesis  The ketone bodies acetoacetate, β-hydroxybutyrate, and acetone are synthesized from acetyl-CoA in the liver when β-oxidation produces acetyl-CoA faster than it can enter the citric acid cycle.

KETONE BODY SYNTHESIS

1. Low insulin levels and high levels of epinephrine stimulate the release of fatty acids from triglycerides stored in adipose tissue.
2. The resulting high rate of β-oxidation in the liver rapidly produces acetyl-CoA.
3. Because much of the compound (oxaloacetate) that combines with acetyl-CoA at the start of the citric acid cycle is being used for gluconeogenesis, acetyl-CoA is being produced faster than it can enter the citric acid cycle and its levels in the liver rise.
4. The excess acetyl-CoA promotes ketone body synthesis (ketogenesis), which begins when two molecules of acetyl-CoA combine. The resulting intermediate is further metabolized to produce acetoacetate.
5. Acetoacetate can be converted into the other two ketone bodies, acetone and β-hydroxybutyrate.

When ketone bodies are used as a source of energy, they are metabolized much like fatty acids in mitochondria. The ketone bodies are broken down to acetyl-CoA and then enter the citric acid cycle. When he was following the ketogenic diet, Charlie Abrahams’ body became filled with ketone bodies, which is one of the goals of the diet. Some evidence suggests that ketone bodies affect brain chemistry in ways that inhibit seizures.
Most of the time, children who are put on the ketogenic diet for epilepsy do so while in a hospital so that staff can teach caregivers about the diet and doctors can monitor the child’s levels of ketones in the blood to ensure that ketogenesis is indeed taking place. The ketogenic diet commonly leads to constipation and acid reflux and can increase the risks for kidney stones, slow growth, and bone fractures, among other things, so children on the diet do need to be closely monitored.

**AMINO ACID METABOLISM**

Amino acids are supplied by our diet as well as by the continual breakdown of body proteins. Although most amino acids in the body are used to synthesize proteins, they are also used to synthesize a variety of other compounds. In many cases, amino acid metabolism requires that they first be stripped of their amino group. The remaining carbon skeleton has several possible fates.

The liver is the major site of amino acid metabolism in the body. In many cases, the amino group is removed from amino acids and then transferred to other compounds in reactions that require a coenzyme synthesized from vitamin B₆. (INFOGRAPHIC 15.14) The transfer of the amino group allows nonessential amino acids to be synthesized. It also prevents the release of large quantities of the amino group, which would accumulate in the body as ammonia and potentially be toxic. Instead, the transfer of the amino group allows the liver to carefully control the release of the amino group so that the ammonia that is produced by removal of the amino group can be effectively converted into the less-toxic waste product urea. Urea is then transported in blood to the kidneys, where it is filtered and then excreted in urine.

**INFOGRAPHIC 15.14**

**Amino Acid Metabolism** Amino acids are metabolized to produce many important compounds. When used as a source of energy or to synthesize glucose or fat, the first step in the metabolism of amino acids is to remove the amino group and transfer it to another chemical compound in a reaction requiring a coenzyme synthesized from vitamin B₆.

Increasing protein intake above a person’s requirement would increase the production of what waste product?
Once the amino group has been removed, the remaining carbon skeleton (chain of carbons) can be used to synthesize glucose when blood glucose is low or fatty acids when excess energy is consumed. To a lesser degree, the carbon skeleton can also be metabolized directly as a source of energy. When used as a direct energy source, the carbon skeletons from various amino acids enter the citric acid cycle at several different points, where they are oxidized to produce reduced coenzymes. As we have seen with the oxidation of pyruvate and fatty acids, the majority of ATP is then produced once the high-energy electrons carried by the reduced coenzymes are transferred to the ETC. Like amino acids, alcohol is metabolized primarily in the liver, as discussed in Chapter 13 and depicted in Infographic 13.6.

**Feasting and Fasting Cycle**

We all experience a daily cycle of feasting and fasting: After we consume our last meal of the day, we fast while we sleep, and then break our fast with our first meal the following day. This daily cycle of feasting and fasting requires pathways of energy metabolism to be carefully coordinated. Excess energy provided by meals (feasting) beyond our immediate needs must be stored (anabolism) so that those stores can subsequently be mobilized (catabolism) to supply energy when fasting. Because pathways of energy storage and mobilization work in opposition to each other, they must be regulated in opposite directions. This regulation is achieved largely by hormones that control the activities of key enzymes in metabolic pathways to coordinate the metabolic adaptations that accompany periods of feasting and fasting.

Insulin, glucagon, and epinephrine are the key hormones involved in the short-term regulation of the metabolic adaptations that occur with feasting and fasting. Insulin is released when meals containing carbohydrates and protein are consumed, and it is the key hormone that stimulates fuel storage. Glucagon and epinephrine are released as blood glucose concentrations drop during a fast, and they are the key hormones that stimulate fuel mobilization. (For more detail on glucose in the body, see Chapter 4.)

**Primary Sites of Hormone Action**

Insulin stimulates glycogen synthesis in the liver and muscle and fat synthesis in the liver. It also inhibits the breakdown of glycogen, fat, and proteins. The primary site of glucagon action is the liver, where it increases glucose production by stimulating glycogen breakdown and glucose synthesis from noncarbohydrate sources (gluconeogenesis). Although epinephrine is often associated with the fight-or-flight response, which requires the mobilization of fuels to supply energy to contracting muscles, it also has an important role in regulating energy metabolism during a fast. Like glucagon, epinephrine stimulates glucose production in the liver. It is also the primary hormone that stimulates the release of fatty acids from triglycerides stored in adipose tissue.

**Feasting and Fasting Cycle: Coordinating Metabolic Adaptations in Pathways of Energy Metabolism**

A meal containing a mix of carbohydrates and protein will stimulate insulin release and promote an anabolic response to increase the synthesis of glycogen, body proteins, and to some degree fatty acids.
Fasting Metabolism: Fuel Mobilization during an Overnight Fast

The principal goals of the metabolic adaptations that occur during an overnight fast are to mobilize fatty acids from triglycerides stored in adipose tissue and to maintain blood glucose concentrations. Although fatty acids can supply all the necessary energy for most tissues, the brain, red blood cells, and a few other tissues must have a steady supply of glucose to function.

As time passes following the last evening meal, blood glucose begins to decrease, causing insulin levels to fall and glucagon and epinephrine levels to rise. Glucagon and epinephrine stimulate the liver to break down stored glycogen to glucose and release it into the blood. While these hormones also stimulate liver gluconeogenesis from carbon sources such as amino acids, this does not occur at high rates until liver glycogen has been significantly depleted.

Epinephrine also activates two lipases in adipose tissue that release fatty acids (lipolysis) from triglycerides stored there. During fasting, fatty acids supply the vast majority of energy for most tissues throughout the body.

Extended Fast—Starvation

As the fast continues, liver glycogen becomes depleted after approximately 24 hours and all glucose must be supplied by gluconeogenesis in the liver, which uses primarily the carbon skeletons from amino acids to provide the oxaloacetate required to synthesize glucose. This results in a rapid loss of skeletal muscle mass and high rates of urea production to dispose of the amino groups that have been stripped from these amino acids.

If a fast is extended and the individual moves into a state of starvation, additional adaptations occur to prolong life. Key among these is the preservation of body proteins.

During a fast, the brain is by far the largest consumer of glucose in the body. Unlike most other tissues, it cannot obtain an appreciable amount of energy from fat, and the brain may account for as much as 20% of all energy used by the body. If an alternative source of energy for the brain were not available, survival would be impossible.
Inborn errors of metabolism are a group of disorders characterized by the blockage of a metabolic pathway. They are caused by mutations (or alterations) in the genes that direct the production of enzymes and the cofactors for metabolism. A mutation causes a gene not to function at all or to function poorly. Most often these altered genes are inherited, from either one or both parents.

In general, the treatment of these metabolic disorders is to minimize or eliminate the buildup of toxic metabolites that result from the block in metabolism while maintaining growth and development. This may be accomplished by special modified diets, supplements, and medications. For example, in the disorder phenylketonuria (PKU), there is a defect in the gene that produces the enzyme that breaks down the amino acid phenylalanine. As a result, that amino acid would be cut dramatically due to the rapid loss of body proteins needed to supply the amino acids from which to synthesize glucose. (INFOGRAPHIC 15.15)

Fortunately, the brain can also meet a significant portion of its energy needs by using ketone bodies produced from fatty acids. Once the period of starvation reaches approximately 10 days, ketone bodies supply about two-thirds of the brain's total energy needs. This adaptation allows protein breakdown to slow as fewer amino acids are used for gluconeogenesis, which in turn significantly prolongs survival time during starvation. Fasting has also been shown to reduce seizures in people with epilepsy, because the body has to rely on ketone bodies rather than glucose for fuel, as happens when following a ketogenic diet. In fact, the use of fasting to control seizures dates back to the time of Hippocrates in ancient Greece, around 400 B.C.

**INFOGRAPHIC 15.15** Summary of Key Hormonal and Metabolic Shifts with Fasting and Feasting

<table>
<thead>
<tr>
<th>Bloods: Key Hormones</th>
<th>Adipose</th>
<th>Muscle (and Other Tissues)</th>
<th>Liver</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>Triglycerides → Fatty acids</td>
<td>Amino acids → Energy</td>
<td>Glucose → Energy</td>
<td>Glucose → Energy</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Protides → Amino acids</td>
<td>Fatty acids → Energy</td>
<td>Amino acids → Glucose</td>
<td>Ketone bodies → Energy</td>
</tr>
<tr>
<td>Insulin</td>
<td>Energy</td>
<td>Fatty acids → Ketone bodies</td>
<td>Fatty acids</td>
<td>Glucose → Energy</td>
</tr>
</tbody>
</table>

**FEASTING ENERGY METABOLISM**

<table>
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<th>Adipose</th>
<th>Muscle (and Other Tissues)</th>
<th>Liver</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>Dietary fats → Triglycerides</td>
<td>Amino acids → Energy</td>
<td>Glucose → Glycogen</td>
<td>Glucose → Energy</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Glucose → Energy</td>
<td>Glucose → Energy</td>
<td>Excess glucose → Triglycerides</td>
<td>Glucose → Energy</td>
</tr>
<tr>
<td>Insulin</td>
<td>Excess glucose</td>
<td>Excess glucose</td>
<td>Ketone bodies</td>
<td>Glucose → Energy</td>
</tr>
</tbody>
</table>

**INBORN ERRORS OF METABOLISM**

During a fast, what is the primary fate of amino acids that are being released from muscles?
Metabolism errors also render some people ineligible to try specialized diets. Children with epilepsy who also have a primary deficiency in the amino acid carnitine, for instance, cannot go on the ketogenic diet because carnitine is required to metabolize fatty acids.

Charlie Abrahams, who is now in his late twenties and a preschool teacher, is still doing very well. In fact, his experience suggests that in some people, the ketogenic diet is not just a treatment for epilepsy but a cure. When he was 5 years old, Charlie was taken off the diet as a test and allowed to eat normally again. His parents watched carefully, monitoring him for seizures—but the seizures never came back. Charlie’s experience isn’t an anomaly.

In 2010, Kossoff, the Johns Hopkins neurologist mentioned earlier, and his colleagues surveyed adults who had followed the ketogenic diet for epilepsy when they were children but who had since given up the diet. They found that 78% of the adults still experienced far fewer seizures than they had before following the diet as children, which suggests that a brief stint on the diet can have long-lasting seizure-reducing effects, for as yet unknown reasons. According to Jim Abrahams, Charlie “eats whatever he wants, and he’s never taken another drug.” Jim believes that because of the ketogenic diet, “There are tons of people like Charlie who’ve had their seizures go away and go on to lead normal lives.”

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accumulates in the body. Individuals with PKU must limit the amount of phenylalanine in their diet for their lifetime. For this reason, products (such as diet sodas) that contain the artificial sweetener aspartame (NutraSweet) must carry a warning label because this sweetener contains phenylalanine.

Another example is maple syrup urine disease, in which the body cannot break down the amino acids leucine, isoleucine, and valine. The urine of people with this condition can smell like maple syrup. If left untreated, this condition typically causes irreversible brain damage and death of the infant, generally within a few months of birth. Long-term treatment consists of a diet that is low in the problematic amino acids.
Metabolic alterations are important
determinants of our health

It is becoming increasingly apparent that undesirable alterations in our metabolism increase the risk of many diseases and, in turn, most diseases dramatically alter our metabolism. For example, disruptions to metabolism are key features in cancer, diabetes, heart and liver diseases, and the declines associated with aging. Even changes in the bacteria that inhabit our gastrointestinal tract can dramatically influence cellular metabolism throughout our bodies in both positive and negative ways. Perhaps one of the more surprising factors that influences our metabolism is our sleep habits. To learn more about how sleep alterations affect our metabolism and health, explore the scientific literature for recent work in this area. Because the scientific literature on this topic can be a bit daunting, we will utilize two sites that provide scientifically sound summaries of recently released studies, EurekAlert! (created by the American Association for the Advancement of Science) and ScienceDaily.

1. You have likely heard of the circadian clock or circadian rhythms—the roughly 24-hour oscillations that regulate a host of body processes, thereby significantly influencing our metabolism. It is becoming increasingly evident that changes in our sleep cycle negatively affect our health because they disrupt our circadian clock and alter our cellular metabolism. Our sleep cycle can be altered by suffering jet lag; working the late shift; or just staying up late studying, binge watching our favorite TV series, or playing video games. To learn more about the startling effects sleep disruptions can have on our health, enter the search terms "sleep loss" health eurekalert into your favorite search engine. It is important to enter “sleep loss” with the quotes as this will search for the intact phrase, rather than each word individually—and this will dramatically improve the specificity of the search. Then make a list of 10 potential negative consequences of poor sleep habits.

2. Recent scientific work has revealed that our bodies run on two circadian clocks—the “master” clock in our brains and a peripheral clock in our body’s organs and tissues, such as the liver, gut, pancreas, and heart. The alterations in the peripheral clock seem to affect our metabolism most profoundly. Visit EurekAlert.org, and enter the search terms peripheral circadian metabolism. Click on several of the news releases that you find in your search, and pick one to read in detail. Then summarize the findings of that study.

3. Not only when we sleep but also when we eat seems to affect our metabolism and health. Time-restricted eating, which limits our food intake to a 10- or 12-hour window of time during the day, seems to improve metabolic health. Search EurekAlert.org for time-restricted eating metabolism, and read one of the studies discussed. Summarize the findings of the study on how time-restricted eating can improve our metabolism and health.
ENERGY METABOLISM: THE INTERACTIONS AND TRANSFORMATIONS OF LIVING CELLS

KEY IDEAS

Metabolism encompasses all the life-sustaining chemical reactions that occur in living organisms that convert one molecule into another molecule. Many metabolic processes fall into one of two broad categories—catabolism and anabolism.

Catabolism is the breakdown of large molecules into smaller ones and is generally accompanied by the release of energy.

Anabolism is the synthesis of large molecules from smaller ones, requiring an input of energy.

The oxidation of our metabolic fuels produces the reduced coenzymes NADH and FADH₂, which carry high-energy electrons to the electron transport chain.

The main pathways involved in capturing some of the energy present in chemical bounds of metabolic fuels to synthesize ATP are glycolysis, beta-oxidation, the citric acid cycle, and the electron transport chain.

Glycolysis and β-oxidation have similar roles in preparing glucose and fatty acids for complete oxidation in the citric acid cycle.

β-Oxidation, the citric acid cycle, and the electron transport chain are aerobic pathways found in the mitochondrial matrix.

The citric acid cycle accepts 2-carbon acetyl groups from acetyl-CoA, which are combined with oxaloacetate to form the 6-carbon compound citrate. Citrate progresses through the citric acid cycle, loses two carbons as CO₂, and is oxidized to re-form oxaloacetate at the end of the cycle.

Acetyl-CoA is produced from the metabolism of glucose, fatty acids, ketone bodies, and some amino acids.

High-energy electrons release energy as they move down the electron transport chain, which is conserved by the pumping of proteins into the mitochondrial intermembrane space. The accumulation of proteins is a source of energy that can be tapped to synthesize ATP.

Amino acids must have their amino group transferred to another molecule before the remaining chain of carbons can be used to synthesize glucose or fatty acids or can be oxidized for energy.

When glycolysis generates NADH faster than it can be reoxidized to NAD⁺ by the electron transport chain, pyruvate must be reduced to lactate, which regenerates the NAD⁺ needed for glycolysis to continue.

Lactate can be used as a substrate for gluconeogenesis in the liver or as a fuel in nonactive skeletal muscles, the heart, and the brain.

During periods of fasting, with severe calorie restriction, or on low-carbohydrate diets, liver glycogen stores will be depleted and gluconeogenesis in the liver will increase to provide the glucose needed by the brain and red blood cells.

Ketone bodies are synthesized from acetyl-CoA from fatty acids when the carbohydrate supply and insulin level are low. The use of ketone bodies by the brain decreases its reliance on glucose for energy, which preserves body proteins because fewer amino acids are needed to supply carbons for gluconeogenesis.
NEED TO KNOW

Review Questions

1. The primary source of the carbons that are incorporated into ketone bodies originate from:
   a. lactate.
   b. oxaloacetate.
   c. pyruvate.
   d. amino acids.
   e. fatty acids.

2. Under conditions that necessitate the conversion of pyruvate into lactate, the purpose of lactate formation is to:
   a. allow the citric acid cycle to proceed.
   b. allow oxygen to be conserved.
   c. allow NADH to be reoxidized.
   d. provide a substrate for gluconeogenesis.

3. What pathway(s) have a direct requirement for O₂? Give the most complete answer.
   a. glycolysis
   b. the ETC
   c. the citric acid cycle
   d. the ETC and citric acid cycle
   e. glycolysis, the ETC, and the citric acid cycle

4. What vitamin is required for the synthesis of any amino acids that our cells are able to make?
   a. B₆
   b. B₁₂
   c. biotin
   d. niacin
   e. riboflavin

5. What is the primary source of energy for red blood cells after 10 days of fasting?
   a. glucose
   b. lactate
   c. fatty acids
   d. ketone bodies

6. What pathway is present in the cytosol?
   a. the electron transport chain
   b. glycolysis
   c. beta-oxidation
   d. the citric acid cycle

7. After about 10 days of fasting, what percentage of the brain’s energy needs is provided by ketone bodies?
   a. 33%
   b. 50%
   c. 66%
   d. 75%
   e. 100%

8. The majority of CO₂ is produced by:
   a. β-oxidation.
   b. glycolysis.
   c. the citric acid cycle.
   d. the ETC.

9. Glycolysis, the electron transport chain, and beta-oxidation all:
   a. consume O₂.
   b. produce ATP.
   c. produce reduced coenzymes.
   d. produce CO₂.

10. Levels of what compound in liver mitochondria must be decreased for ketogenesis to proceed rapidly?
    a. acetyl-CoA
    b. glucose
    c. oxaloacetate
    d. NAD⁺
    e. fatty acids