Chapter 8

An Introduction to Metabolism

Lecture Outline

Overview: The Energy of Life

Concept 8.1 An organism's metabolism transforms matter and energy, subject to the laws of thermodynamics

- The totality of an organism's chemical reactions is called **metabolism**.

- Metabolism is an emergent property of life that arises from interactions between molecules within the orderly environment of the cell.

The chemistry of life is organized into metabolic pathways.

- Metabolic pathways begin with a specific molecule, which is then altered in a series of defined steps to form a specific product.

- A specific enzyme catalyzes each step of the pathway.

- Catabolic pathways release energy by breaking down complex molecules to simpler compounds.
  - ° A major pathway of catabolism is cellular respiration, in which the sugar glucose is broken down in the presence of oxygen to carbon dioxide and water.

- **Anabolic pathways** consume energy to build complicated molecules from simpler compounds. They are also called biosynthetic pathways.
  - ° The synthesis of protein from amino acids is an example of anabolism.

- The energy released by catabolic pathways can be stored and then used to drive anabolic pathways.

- Energy is fundamental to all metabolic processes, and therefore an understanding of energy is key to understanding how the living cell works.
  - ° **Bioenergetics** is the study of how organisms manage their energy resources.

Organisms transform energy.

- **Energy** is the capacity to do work.
  - ° Energy exists in various forms, and cells transform energy from one type into another.

- **Kinetic energy** is the energy associated with the relative motion of objects.
  - ° Objects in motion can perform work by imparting motion to other matter.
  - ° Photons of light can be captured and their energy harnessed to power photosynthesis in green plants.
  - ° **Heat** or **thermal energy** is kinetic energy associated with the random movement of atoms or molecules.

- **Potential energy** is the energy that matter possesses because of its location or structure.

- ° **Chemical energy** is a form of potential energy stored in molecules because of the arrangement of their atoms.
- Energy can be converted from one form to another.
  - ° For example, as a boy climbs stairs to a diving platform, he is releasing chemical energy stored in his cells from the food he ate for lunch.
  - ° The kinetic energy of his muscle movement is converted into potential energy as he climbs higher.
  - ° As he dives, the potential energy is converted back to kinetic energy.
  - ° Kinetic energy is transferred to the water as he enters it.
  - ° Some energy is converted to heat due to friction.

The energy transformations of life are subject to two laws of thermodynamics.

- **Thermodynamics** is the study of energy transformations.
- In this field, the term *system* refers to the matter under study and the *surroundings* include everything outside the system.
- A *closed system,* approximated by liquid in a thermos, is isolated from its surroundings.
- In an *open system,* energy and matter can be transferred between the system and its surroundings.
- Organisms are open systems.
  - ° They absorb energy—light or chemical energy in the form of organic molecules—and release heat and metabolic waste products such as urea or CO_2 to their surroundings.
- The **first law of thermodynamics** states that energy can be transferred and transformed, but it cannot be created or destroyed.
  - ° The first law is also known as the *principle of conservation of energy.*
  - ° Plants do not produce energy; they transform light energy to chemical energy.
- During every transfer or transformation of energy, some energy is converted to heat, which is the energy associated with the random movement of atoms and molecules.
- A system can use heat to do work only when there is a temperature difference that results in heat flowing from a warmer location to a cooler one.
  - ° If temperature is uniform, as in a living cell, heat can only be used to warm the organism.
- Energy transfers and transformations make the universe more disordered due to this loss of usable energy.
- **Entropy** is a quantity used as a measure of disorder or randomness.
  - ° The more random a collection of matter, the greater its entropy.
- The **second law of thermodynamics** states that every energy transfer or transformation increases the entropy of the universe.
  - ° While order can increase locally, there is an unstoppable trend toward randomization of the universe.
  - ° Much of the increased entropy of the universe takes the form of increasing heat, which is the energy of random molecular motion.
- In most energy transformations, ordered forms of energy are converted at least partly to heat.
  - ° Automobiles convert only 25% of the energy in gasoline into motion; the rest is lost as heat.
  - ° Living cells unavoidably convert organized forms of energy to heat.

- For a process to occur on its own, without outside help in the form of energy input, it must increase the entropy of the universe.
- The word *spontaneous* describes a process that can occur without an input of energy.
  - ° Spontaneous processes need not occur quickly.
  - ° Some spontaneous processes are instantaneous, such as an explosion. Some are very slow, such as the rusting of an old car.
- Another way to state the second law of thermodynamics is for a process to occur spontaneously, it must increase the entropy of the universe.
- Living systems create ordered structures from less ordered starting materials.
  - ° For example, amino acids are ordered into polypeptide chains.
  - ° The structure of a multicellular body is organized and complex.
- However, an organism also takes in organized forms of matter and energy from its surroundings and replaces them with less ordered forms.
  - ° For example, an animal consumes organic molecules as food and catabolizes them to low-energy carbon dioxide and water.
- Over evolutionary time, complex organisms have evolved from simpler ones.
  - ° This increase in organization does not violate the second law of thermodynamics.
  - ° The entropy of a particular system, such as an organism, may decrease as long as the total entropy of the *universe*—the system plus its surroundings—increases.
  - ° Organisms are islands of low entropy in an increasingly random universe.
  - ° The evolution of biological order is perfectly consistent with the laws of thermodynamics.

Concept 8.2 The free-energy change of a reaction tells us whether the reaction occurs spontaneously

- How can we determine which reactions occur spontaneously and which ones require an input of energy?
- The concept of free energy provides a useful function for measuring spontaneity of a system.
- **Free energy** is the portion of a system's energy that is able to perform work when temperature and pressure is uniform throughout the system, as in a living cell.
- The free energy (G) in a system is related to the total *enthalpy* (in biological systems, equivalent to energy) (H) and the entropy (S) by this relationship:
  - ° $G = H - TS$, where T is temperature in Kelvin units.
  - ° Increases in temperature amplify the entropy term.
  - ° Not all the energy in a system is available for work because the entropy component must be subtracted from the enthalpy component.
  - ° What remains is the free energy that is available for work.
- Free energy can be thought of as a measure of the stability of a system.
  - ° Systems that are high in free energy—compressed springs, separated charges, organic polymers—are unstable and tend to move toward a more stable state, one with less free energy.
  - ° Systems that tend to change spontaneously are those that have high enthalpy, low entropy, or both.

- In any spontaneous process, the free energy of a system decreases.
- We can represent this change in free energy from the start of a process until its finish by:
  ° $\Delta G = G_{\text{final state}} - G_{\text{starting state}}$
  ° Or $\Delta G = \Delta H - T\Delta S$
- For a process to be spontaneous, the system must either give up enthalpy (decrease in H), give up order (increase in S), or both.
  ° ΔG must be negative for a process to be spontaneous.
    ▪ Every spontaneous process is characterized by a decrease in the free energy of the system.
    ▪ Processes that have a positive or zero ΔG are never spontaneous.
  ° The greater the decrease in free energy, the more work a spontaneous process can perform.
  ° Nature runs "downhill."
- A system at equilibrium is at maximum stability.
  ° In a chemical reaction at equilibrium, the rates of forward and backward reactions are equal, and there is no change in the concentration of products or reactants.
  ° At equilibrium $\Delta G = 0$, and the system can do no work.
  ° A process is spontaneous and can perform work only when it is moving toward equilibrium.
  ° Movements away from equilibrium are nonspontaneous and require the addition of energy from an outside energy source (the surroundings).
- Chemical reactions can be classified as either exergonic or endergonic based on free energy.
- An **exergonic reaction** proceeds with a net release of free energy; ΔG is negative.
- The magnitude of ΔG for an exergonic reaction is the maximum amount of work the reaction can perform.
- The greater the decrease in free energy, the greater the amount of work that can be done.
  ° For the overall reaction of cellular respiration: $C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$
    ▪ $\Delta G = -686$ kcal/mol
  ° For each mole (180 g) of glucose broken down by respiration, 686 kcal of energy are made available to do work in the cell.
    ▪ The products have 686 kcal less free energy than the reactants.
- An **endergonic reaction** is one that absorbs free energy from its surroundings.
  ° Endergonic reactions store energy in molecules; ΔG is positive.
  ° Endergonic reactions are nonspontaneous, and the magnitude of ΔG is the quantity of energy required to drive the reaction.
- If cellular respiration releases 686 kcal, then photosynthesis, the reverse reaction, must require an equivalent investment of energy.
  ° For the conversion of carbon dioxide and water to sugar, $\Delta G = +686$ kcal/mol.
- Photosynthesis is strongly endergonic, powered by the absorption of light energy.
- Reactions in a closed system eventually reach equilibrium and can do no work.
  ° A cell that has reached metabolic equilibrium has a $\Delta G = 0$ and is dead!
- Metabolic disequilibrium is one of the defining features of life.

- Cells maintain disequilibrium because they are open systems. The constant flow of materials into and out of the cell keeps metabolic pathways from ever reaching equilibrium.
  ° A cell continues to do work throughout its life.
- A catabolic process in a cell releases free energy in a series of reactions, not in a single step.
- Some reversible reactions of respiration are constantly "pulled" in one direction, as the product of one reaction does not accumulate but becomes the reactant in the next step.
- Sunlight provides a daily source of free energy for photosynthetic organisms.
- Nonphotosynthetic organisms depend on a transfer of free energy from photosynthetic organisms in the form of organic molecules.

Concept 8.3 ATP powers cellular work by coupling exergonic reactions to endergonic reactions

- A cell does three main kinds of work:
  1. Mechanical work, such as the beating of cilia, contraction of muscle cells, and movement of chromosomes during cellular reproduction.
  2. Transport work, the pumping of substances across membranes against the direction of spontaneous movement.
  3. Chemical work, driving endergonic reactions such as the synthesis of polymers from monomers.
- Cells manage their energy resources to do this work by **energy coupling,** the use of an exergonic process to drive an endergonic one.
- In most cases, the immediate source of energy to power cellular work is ATP.
- **ATP (adenosine triphosphate)** is a type of nucleotide consisting of the nitrogenous base adenine, the sugar ribose, and a chain of three phosphate groups.
- The bonds between phosphate groups can be broken by hydrolysis.
  ° Hydrolysis of the end phosphate group forms adenosine diphosphate.
    ▪ ATP -> ADP + P$_i$
    ▪ This reaction releases 7.3 kcal of energy per mole of ATP under standard conditions (1 M of each reactant and product, 25°C, pH 7).
  ° In the cell, ΔG for hydrolysis of ATP is about −13 kcal/mol.
- While the phosphate bonds of ATP are sometimes referred to as high-energy phosphate bonds, these are actually fairly weak covalent bonds.
  ° However, they are unstable, and their hydrolysis yields energy because the products are more stable.
- The release of energy during the hydrolysis of ATP comes from the chemical change to a state of lower free energy, not from the phosphate bonds themselves.
- Why does the hydrolysis of ATP yield so much energy?
  ° Each of the three phosphate groups has a negative charge.
  ° These three like charges are crowded together, and their mutual repulsion contributes to the instability of this region of the ATP molecule.
- In the cell, the energy from the hydrolysis of ATP is directly coupled to endergonic processes by the transfer of the phosphate group to another molecule.

- °   This recipient molecule is now **phosphorylated.**
- °   This molecule is now more reactive (less stable) than the original unphosphorylated molecules.
- Mechanical, transport, and chemical work in the cell are nearly always powered by the hydrolysis of ATP.
  - °   In each case, a phosphate group is transferred from ATP to another molecule and the phosphorylated molecule undergoes a change that performs work.
- ATP is a renewable resource that can be regenerated by the addition of a phosphate group to ADP.
  - °   The energy to phosphorylate ADP comes from catabolic reactions in the cell.
  - °   A working muscle cell recycles its entire pool of ATP once each minute.
  - °   More than 10 million ATP molecules are consumed and regenerated per second per cell.
- Regeneration of ATP is an endergonic process, requiring an investment of energy.
  - ° $\Delta G = 7.3$ kcal/mol.
- Catabolic (exergonic) pathways, especially cellular respiration, provide the energy for the exergonic regeneration of ATP.
- The chemical potential energy temporarily stored in ATP drives most cellular work.

Concept 8.4 Enzymes speed up metabolic reactions by lowering energy barriers

- Spontaneous chemical reactions may occur so slowly as to be imperceptible.
  - °   The hydrolysis of table sugar (sucrose) to glucose and fructose is exergonic.
    - ▪ $\Delta G = -7$ kcal/mol
  - °   Despite this, your sugar sits in its bowl with no observable hydrolysis.
  - °   If we add a small amount of the enzyme catalyst sucrase to a solution of sugar, all the sucrose will be hydrolyzed within seconds.
- A **catalyst** is a chemical agent that speeds up the rate of a reaction without being consumed by the reaction.
  - °   An **enzyme** is a catalytic protein.
- Enzymes regulate metabolic pathways.
- Every chemical reaction involves bond breaking and bond forming.
  - °   To hydrolyze sucrose, the bond between glucose and fructose must be broken and new bonds must form with hydrogen and hydroxyl ions from water.
- To reach a state where bonds can break and reform, reactant molecules must absorb energy from their surroundings. When the new bonds of the product molecules form, energy is released as heat as the molecules assume stable shapes with lower energy.
- The initial investment of energy for starting a reaction is the **free energy of activation** or **activation energy** (E_A).
- Activation energy is the amount of energy necessary to push the reactants over an energy barrier so that the reaction can proceed.
  - °   At the summit, the molecules are in an unstable condition, the *transition state.*
  - °   Activation energy may be supplied in the form of heat that the reactant molecules absorb from the surroundings.

- The bonds of the reactants break only when the molecules have absorbed enough energy to become unstable and, therefore, more reactive.
- The absorption of thermal energy increases the speed of the reactant molecules, so they collide more often and more forcefully.
- Thermal agitation of the atoms in the molecules makes bonds more likely to break.
- As the molecules settle into new, stable bonding arrangements, energy is released to the surroundings.
- In exergonic reactions, the activation energy is released back to the surroundings, and additional energy is released with the formation of new bonds.

- For some processes, E_A is not high, and the thermal energy provided by room temperature is sufficient for many reactants to reach the transition state.

- In many cases, E_A is high enough that the transition state is rarely reached and that the reaction hardly proceeds at all. In these cases, the reaction will only occur at a noticeable rate if the reactants are heated.
  - A spark plug provides the energy to energize a gasoline-oxygen mixture and cause combustion.
  - Without that activation energy, the hydrocarbons of gasoline are too stable to react with oxygen.

- Proteins, DNA, and other complex organic molecules are rich in free energy. Their hydrolysis is spontaneous, with the release of large amounts of energy.
  - However, there is not enough energy at the temperatures typical of the cell for the vast majority of organic molecules to make it over the hump of activation energy.

- How are the barriers for selected reactions surmounted to allow cells to carry out the processes of life?
  - Heat would speed up reactions, but it would also denature proteins and kill cells.

- Enzymes speed reactions by lowering E_A.
  - The transition state can then be reached even at moderate temperatures.

- Enzymes do not change ΔG.
  - They hasten reactions that would occur eventually.
  - Because enzymes are so selective, they determine which chemical processes will occur at any time.

Enzymes are substrate specific.

- The reactant that an enzyme acts on is the **substrate.**

- The enzyme binds to a substrate, or substrates, forming an **enzyme-substrate complex.**

- While the enzyme and substrate are bound, the catalytic action of the enzyme converts the substrate to the product or products.

- The reaction catalyzed by each enzyme is very specific.

- What accounts for this molecular recognition?
  - The specificity of an enzyme results from its three-dimensional shape.

- Only a portion of the enzyme binds to the substrate.
  - The **active site** of an enzyme is typically a pocket or groove on the surface of the protein into which the substrate fits.
  - The active site is usually formed by only a few amino acids.

- The specificity of an enzyme is due to the fit between the active site and the substrate.
- As the substrate enters the active site, interactions between the substrate and the amino acids of the protein causes the enzyme to change shape slightly, leading to a tighter **induced fit** that brings chemical groups in position to catalyze the reaction.

The active site is an enzyme's catalytic center.

- In most cases, substrates are held in the active site by weak interactions, such as hydrogen bonds and ionic bonds.
  - ° R groups of a few amino acids on the active site catalyze the conversion of substrate to product.
  - ° The product then leaves the active site.
- A single enzyme molecule can catalyze thousands of reactions a second.
- Enzymes are unaffected by the reaction and are reusable.
- Most metabolic enzymes can catalyze a reaction in both the forward and reverse directions.
  - ° The actual direction depends on the relative concentrations of products and reactants.
  - ° Enzymes catalyze reactions in the direction of equilibrium.
- Enzymes use a variety of mechanisms to lower activation energy and speed up a reaction.
  - ° In reactions involving more than one reactant, the active site brings substrates together in the correct orientation for the reaction to proceed.
  - ° As the active site binds the substrate, it may put stress on bonds that must be broken, making it easier for the reactants to reach the transition state.
  - ° R groups at the active site may create a microenvironment that is conducive to a specific reaction.
    - ▪ An active site may be a pocket of low pH, facilitating H^+ transfer to the substrate as a key step in catalyzing the reaction.
  - ° Enzymes may briefly bind covalently to substrates.
    - ▪ Subsequent steps of the reaction restore the R groups within the active site to their original state.
- The rate that a specific number of enzymes convert substrates to products depends in part on substrate concentrations.
  - ° At low substrate concentrations, an increase in substrate concentration speeds binding to available active sites.
  - ° However, there is a limit to how fast a reaction can occur.
  - ° At high substrate concentrations, the active sites on all enzymes are engaged.
    - ▪ The enzyme is *saturated.*
    - ▪ The rate of the reaction is determined by the speed at which the active site can convert substrate to product.
- The only way to increase productivity at this point is to add more enzyme molecules.

A cell's physical and chemical environment affects enzyme activity.

- The activity of an enzyme is affected by general environmental conditions, such as temperature and pH.
- Each enzyme works best at certain *optimal conditions,* which favor the most active conformation for the enzyme molecule.
- Temperature has a major impact on reaction rate.

- ° As temperature increases, collisions between substrates and active sites occur more frequently as molecules move more rapidly.
- ° As temperature increases further, thermal agitation begins to disrupt the weak bonds that stabilize the protein's active conformation, and the protein denatures.
- ° Each enzyme has an optimal temperature.
    - ▪ Most human enzymes have optimal temperatures of about 35–40°C.
    - ▪ Bacteria that live in hot springs contain enzymes with optimal temperatures of 70°C or above.
- Each enzyme also has an optimal pH.
- Maintenance of the active conformation of the enzyme requires a particular pH.
    - ° This falls between pH 6 and 8 for most enzymes.
    - ° However, digestive enzymes in the stomach are designed to work best at pH 2, while those in the intestine have an optimum of pH 8.
- Many enzymes require nonprotein helpers, called **cofactors,** for catalytic activity.
    - ° Cofactors bind permanently or reversibly to the enzyme.
    - ° Some inorganic cofactors include zinc, iron, and copper.
- Organic cofactors are called **coenzymes.**
    - ° Many vitamins are coenzymes.
- Binding by inhibitors prevents enzymes from catalyzing reactions.
    - ° If inhibitors attach to the enzyme by covalent bonds, inhibition may be irreversible.
    - ° If inhibitors bind by weak bonds, inhibition may be reversible.
- Some reversible inhibitors resemble the substrate and compete for binding to the active site.
    - ° These molecules are called **competitive inhibitors.**
    - ° Competitive inhibition can be overcome by increasing the concentration of the substrate.
- **Noncompetitive inhibitors** impede enzymatic reactions by binding to another part of the molecule.
    - ° Binding by the inhibitor causes the enzyme to change shape, rendering the active site less effective at catalyzing the reaction.
- Toxins and poisons are often irreversible enzyme inhibitors.
- Sarin is the nerve gas that was released by terrorists in the Tokyo subway in 1995.
    - ° Sarin binds covalently to the R group on the amino acid serine.
    - ° Serine is found in the active site of acetylcholinesterase, an important nervous system enzyme.

Concept 8.5 Regulation of enzyme activity helps control metabolism

Metabolic control often depends on allosteric regulation.

- In many cases, the molecules that naturally regulate enzyme activity behave like reversible noncompetitive inhibitors.
- Regulatory molecules often bind weakly to an **allosteric site,** a specific receptor on the enzyme away from the active site.
    - ° Binding by these molecules can either inhibit or stimulate enzyme activity.

- Most allosterically regulated enzymes are constructed of two or more polypeptide chains.
  ° Each subunit has its own active site.
  ° Allosteric sites are often located where subunits join.
- The binding of an *activator* stabilizes the conformation that has functional active sites, while the binding of an *inhibitor* stabilizes the inactive form of the enzyme.
- As the chemical conditions in the cell shift, the pattern of allosteric regulation may shift as well.
- By binding to key enzymes, reactants and products of ATP hydrolysis may play a major role in balancing the flow of traffic between anabolic and catabolic pathways.
  ° For example, ATP binds to several catabolic enzymes allosterically, inhibiting their activity by lowering their affinity for substrate.
  ° ADP functions as an activator of the same enzymes.
  ° ATP and ADP also affect key enzymes in anabolic pathways.
  ° In this way, allosteric enzymes control the rates of key reactions in metabolic pathways.
- In enzymes with multiple catalytic subunits, binding by a substrate to one active site stabilizes favorable conformational changes at all other subunits, a process called **cooperativity.**
  ° This mechanism amplifies the response of enzymes to substrates, priming the enzyme to accept additional substrates.
- A common method of metabolic control is **feedback inhibition** in which an early step in a metabolic pathway is switched off by the pathway's final product.
  ° The product acts as an inhibitor of an enzyme in the pathway.
- Feedback inhibition prevents a cell from wasting chemical resources by synthesizing more product than is needed.

The localization of enzymes within a cell helps order metabolism.

- Structures within the cell help bring order to metabolic pathways.
- A team of enzymes for several steps of a metabolic pathway may be assembled as a multienzyme complex.
- The product from the first reaction can then pass quickly to the next enzyme until the final product is released.
- Some enzymes and enzyme complexes have fixed locations within the cells as structural components of particular membranes.
  ° Others are confined within membrane-enclosed eukaryotic organelles.
- Metabolism, the intersecting set of chemical pathways characteristic of life, is a choreographed interplay of thousands of different kinds of cellular molecules.