Bioenergetics: The Role of ATP

BIOMEDICAL IMPORTANCE

Bioenergetics, or biochemical thermodynamics, is the study of the energy changes accompanying biochemical reactions. Biologic systems are essentially **isothermic** and use chemical energy to power living processes.How an animal obtains suitable fuel from its food to provide this energy is basic to the understanding of normal nutrition and metabolism. Death from **starvation** occurs when available energy reserves are depleted, and certain forms of malnutrition are associated with energy imbalance **(marasmus).** Thyroid hormones control the rate of energy release (metabolic rate), and disease results when they malfunction. Excess storage of surplus energy causes **obesity,** one of the most common diseases of Western society.

FREE ENERGY IS THE USEFUL ENERGY IN A SYSTEM

Gibbs change in free energy (ΔG) is that portion of the total energy change in a system that is available for doing work—ie, the useful energy, also known as the chemical potential.

Biologic Systems Conform to the General Laws of Thermodynamics

The first law of thermodynamics states that **the total energy of a system, including its surroundings, remains constant.** It implies that within the total system, energy is neither lost nor gained during any change. However, energy may be transferred from one part of the system to another or may be transformed into another form of energy. In living systems, chemical energy may be transformed into heat or into electrical, radiant, or mechanical energy.

The second law of thermodynamics states that **the total entropy of a system must increase if a process is to occur spontaneously. Entropy** is the extent of disorder or randomness of the system and becomes maximum as equilibrium is

approached. Under conditions of constant temperature and pressure, the relationship between the free energy change (ΔG) of a reacting
system and the change in entropy (ΔS) is expressed by the following equation, which combines
the two laws of thermodynamics: $\Delta G = \Delta H - T\Delta S$
where ΔH is the change in **enthalpy** (heat) and T is the absolute temperature. In biochemical reactions, because ΔH is approximately equal to ΔE, the total change in internal energy of the reaction, the above relationship may be expressed in the following way: $\Delta G = \Delta E - T\Delta S$

If ΔG is negative, the reaction proceeds spontaneously with loss of free energy; ie, it is **exergonic.** If, in addition, ΔG is of great magnitude, the reaction goes virtually to completion and is essentially irreversible. On the other hand, if ΔG is positive, the reaction proceeds only if free energy can be gained; ie, it is **endergonic.** If, in addition, the magnitude of ΔG is great, the system is stable, with little or no tendency for a reaction to occur. If ΔG is zero, the system is at equilibrium and no net change takes place. When the reactants are present in concentrations of 1.0 mol/L, ΔG0 is the standard free energy change. For biochemical reactions, a standard state is defined as having a pH of 7.0. The standard free energy change at this standard state is denoted by ΔG0'.

ENDERGONIC PROCESSES PROCEED BY COUPLING TO EXERGONIC PROCESSES

The vital processes—eg, synthetic reactions, muscular contraction, nerve impulse conduction, and active transport—obtain energy by chemical linkage, or **coupling,** to oxidative reactions. In its simplest form, this type of coupling may be represented as shown in **Figure 1**. The conversion of metabolite A to metabolite B occurs with release of free energy and is coupled to another reaction in which free energy is required to convert metabolite C to metabolite D. The terms **exergonic** and **endergonic,** rather than the normal chemical terms "exothermic" and "endothermic," are used to indicate that a process is accompanied by loss or gain, respectively, of free energy in any form, not necessarily as heat. In practice, an endergonic process cannot exist independently, but must be a component of a coupled exergonic–endergonic system where the overall net change is exergonic.

The exergonic reactions are termed **catabolism** (generally, the breakdown or oxidation of fuel molecules), whereas the synthetic reactions that build up substances are termed **anabolism.** The combined catabolic and anabolic processes constitute **metabolism.**

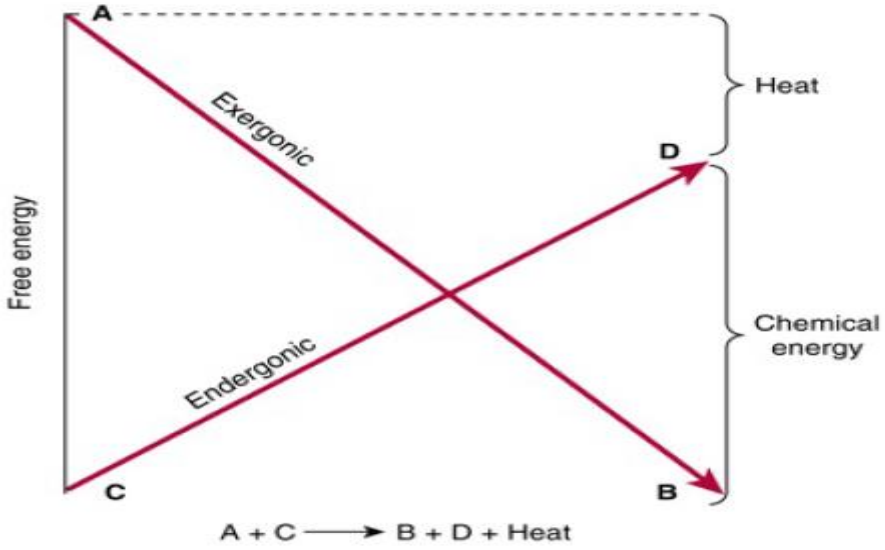


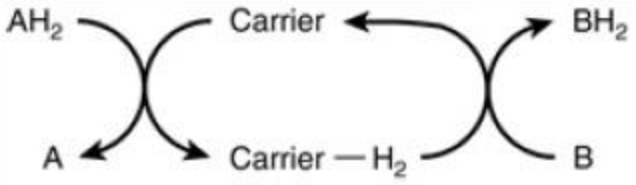
Figure 1: Coupling of an exergonic to an endergonic reaction.

If the reaction shown in **Figure 1** is to go from left to right, then the overall process must be accompanied by loss of free energy as heat. One possible mechanism of coupling
could be envisaged if a common obligatory intermediate (I) took part in both reactions, ie,

$$A + C \rightarrow I \rightarrow B + D$$

Some exergonic and endergonic reactions in biologic systems are coupled in this way. This type of system has a built-in mechanism for biologic control of the rate of oxidative processes since the common obligatory intermediate allows the rate of utilization of the product of the synthetic path (D) to determine by mass action the rate at which A is oxidized. Indeed, these relationships supply a basis for the concept of **respiratory control,** the process that prevents an organism from burning out of control. An extension of the coupling concept is provided by dehydrogenation reactions, which are coupled to hydrogenations by an intermediate carrier (**Figure11- 2**).

Figure 11–2

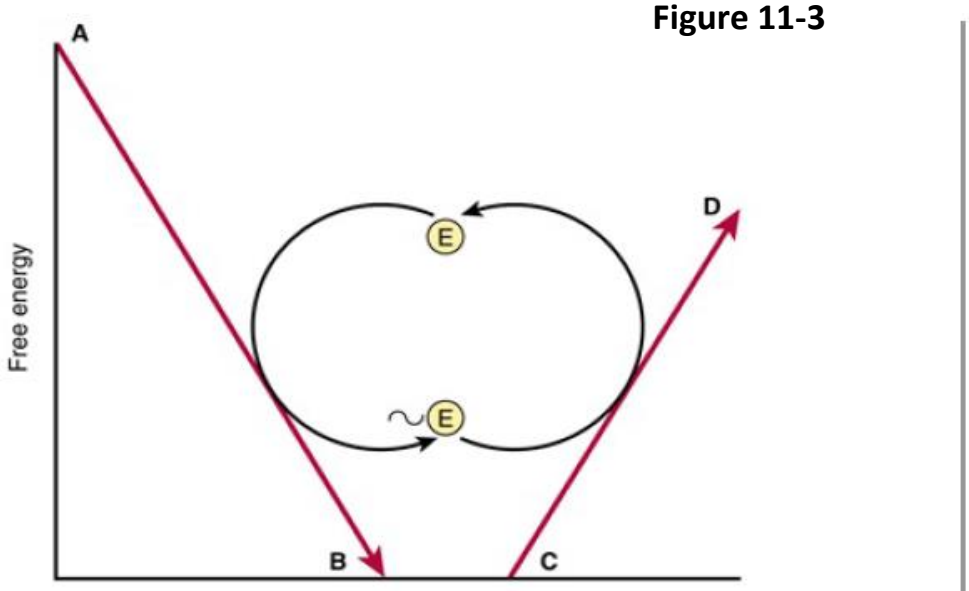


Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 29th Edition*: www.accessmedicine.com

Coupling of dehydrogenation and hydrogenation reactions by an intermediate carrier.

An alternative method of coupling an exergonic to an endergonic process is to synthesize a compound of high-energy potential in the exergonic reaction and to incorporate this new compound into the endergonic reaction, thus effecting a transference of free energy from the exergonic to the endergonic pathway (**Figure 11–3**). The biologic advantage of this mechanism is that the compound of high potential energy, ~Ⓔ, unlike I in the previous system, need not be structurally related to A, B, C, or D, allowing Ⓔ to serve as a transducer of energy from a wide range of exergonic reactions to an equally wide range of endergonic reactions or processes, such as biosyntheses, muscular contraction, nervous excitation, and active transport. In the living cell, the principal high-energy intermediate or carrier compound (designated ~Ⓔ in **Figure 11–3**) is **adenosine triphosphate (ATP)** (**Figure 11–4**).

Figure 11-3



Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 29th Edition*: www.accessmedicine.com

Transfer of free energy from an exergonic to an endergonic reaction via a high-energy intermediate compound (~Ⓔ).

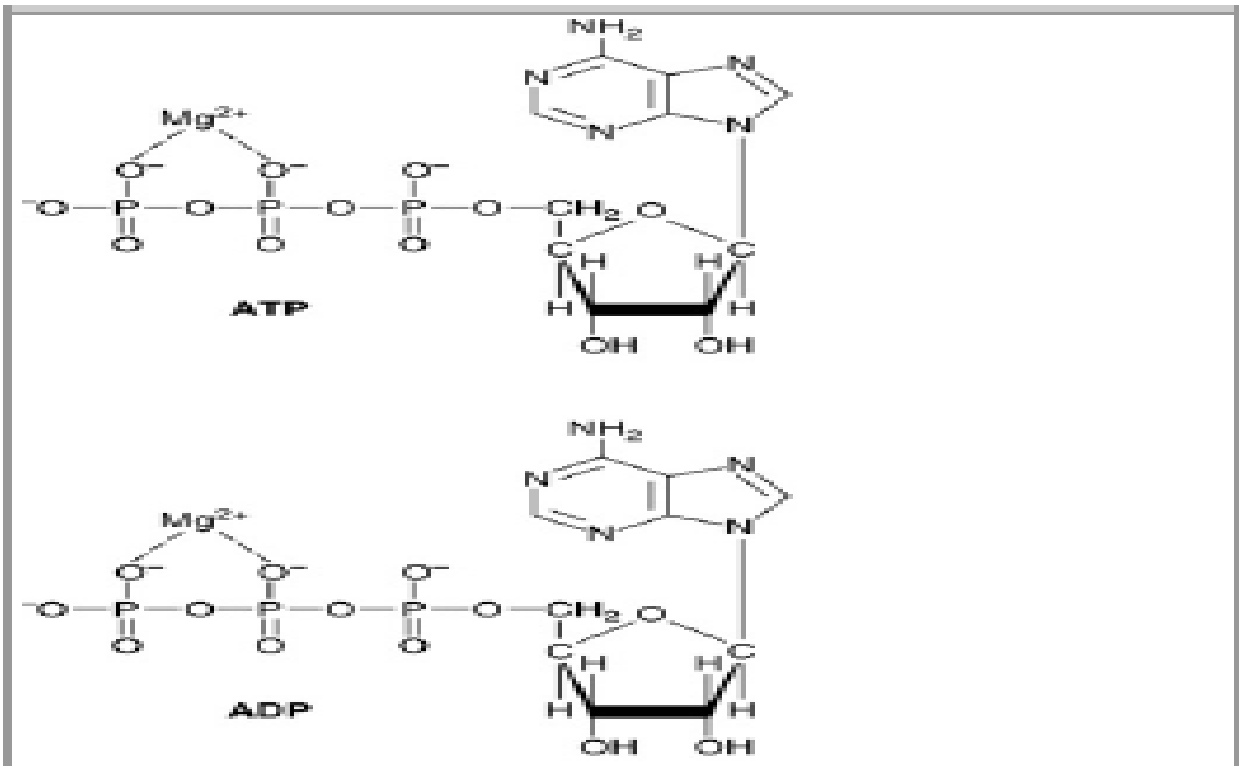


Figure 11-4

HIGH-ENERGY PHOSPHATES PLAY A CENTRAL ROLE IN ENERGY CAPTURE AND TRANSFER

In order to maintain living processes, all organisms must obtain supplies of free energy from their environment. **Autotrophic** organisms utilize simple exergonic processes; eg, the energy of sunlight (green plants), the reaction Fe2+ to Fe3+ (some bacteria). On the other hand, **heterotrophic** organisms obtain free energy by coupling their metabolism to the breakdown of complex organic molecules in their environment. In all these organisms, ATP plays a central role in the transference of free energy from the exergonic to the endergonic processes (**Figure 11–3**). ATP is a nucleoside triphosphate containing adenine, ribose, and three phosphate groups. In its reactions in the cell, it functions as the Mg2+ complex (**Figure 11–4**).

The Intermediate Value for the Free Energy of Hydrolysis of ATP Has Important Bioenergetic Significance

The standard free energy of hydrolysis of a number of biochemically important phosphates is shown in **Table 11–1**. An estimate of the comparative tendency of each of the phosphate groups to transfer to a suitable acceptor may be obtained from the Δ*G*0' of hydrolysis at 37°C. The value for the hydrolysis of the terminal phosphate of ATP divides the list into two groups. **Low-energy phosphates,** exemplified by the ester phosphates found in the intermediates of glycolysis, have *G*0' values smaller than that of ATP, while in **high-energy phosphates** the value is higher than that of ATP. The components of this latter group, including ATP, are usually anhydrides (eg, the 1-phosphate of 1,3-bisphosphoglycerate), enolphosphates (eg, phosphoenolpyruvate), and phosphoguanidines (eg, creatine phosphate, arginine phosphate).

Table 11–1 Standard Free Energy of Hydrolysis of Some Organophosphates of Biochemical Importance

	$-\Delta G^{0'}$	
Compound	**kJ/mol**	**kcal/mol**
Phosphoenolpyruvate	-61.9	-14.8
Carbamoyl phosphate	-51.4	-12.3
1,3-Bisphosphoglycerate (to 3-phosphoglycerate)	-49.3	-11.8
Creatine phosphate	-43.1	-10.3
ATP $\rightarrow$ AMP + PPi	-32.2	-7.7
ATP $\rightarrow$ ADP + P_i	-30.5	-7.3
Glucose 1-phosphate	-20.9	-5.0
PPi	-19.2	-4.6
Fructose 6-phosphate	-15.9	-3.8
Glucose 6-phosphate	-13.8	-3.3
Glycerol 3-phosphate	-9.2	-2.2

The symbol ~Ⓟ indicates that the group attached to the bond, on transfer to an appropriate acceptor, results in transfer of the larger quantity of free energy. For this reason, the term **group transfer potential,** rather than "high-energy bond," is

preferred by some. Thus, ATP contains two high-energy phosphate groups and ADP contains one, whereas the phosphate in AMP (adenosine monophosphate) is of the low-energy type since it is a normal ester link (**Figure 11–5**).

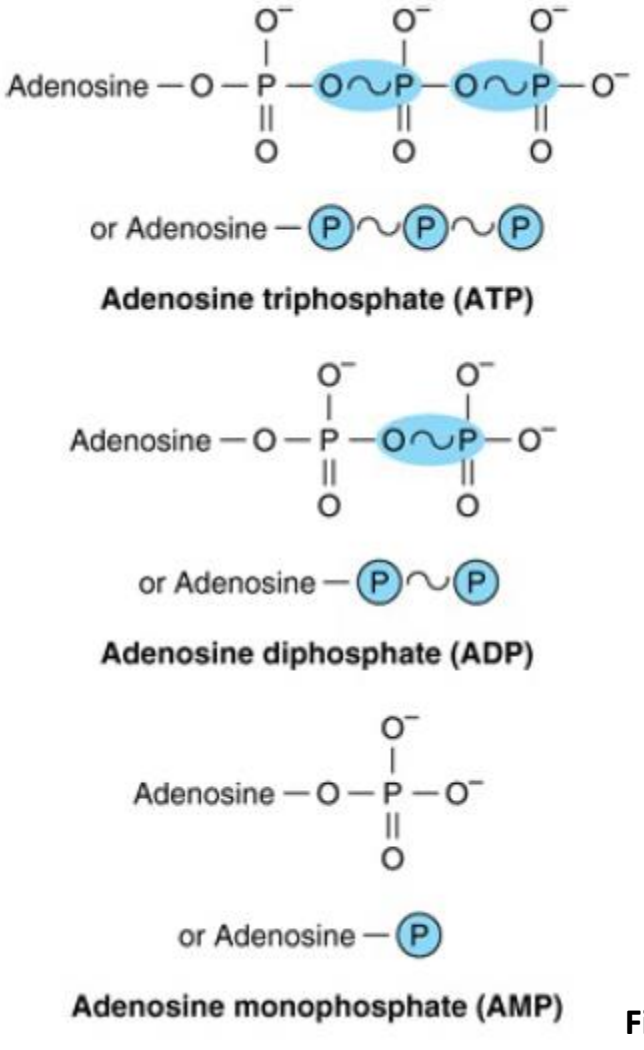


Figure 11-5

The intermediate position of ATP allows it to play an important role in energy transfer. The high free-energy change on hydrolysis of ATP is due to relief of charge repulsion of adjacent negatively charged oxygen atoms and to stabilization of the reaction products, especially phosphate, as resonance hybrids (**Figure 11–6**). Other "high-energy compounds" are thiol esters involving coenzyme A (eg, acetyl-CoA), acyl carrier protein, amino acid esters involved in protein synthesis, *S*-adenosylmethionine (active methionine), UDPGlc (uridine diphosphate glucose), and PRPP (5-phosphoribosyl-1-pyrophosphate).

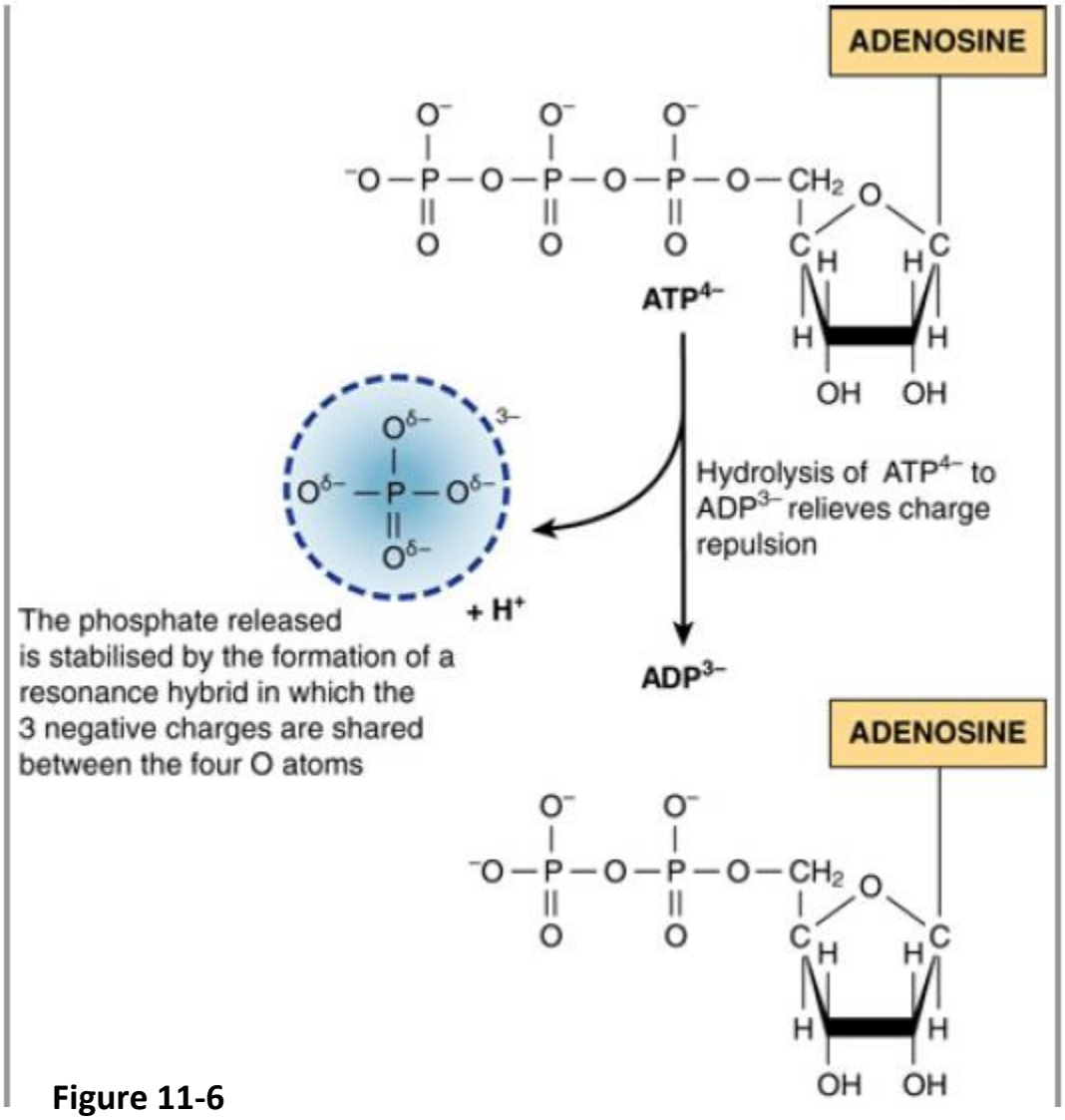
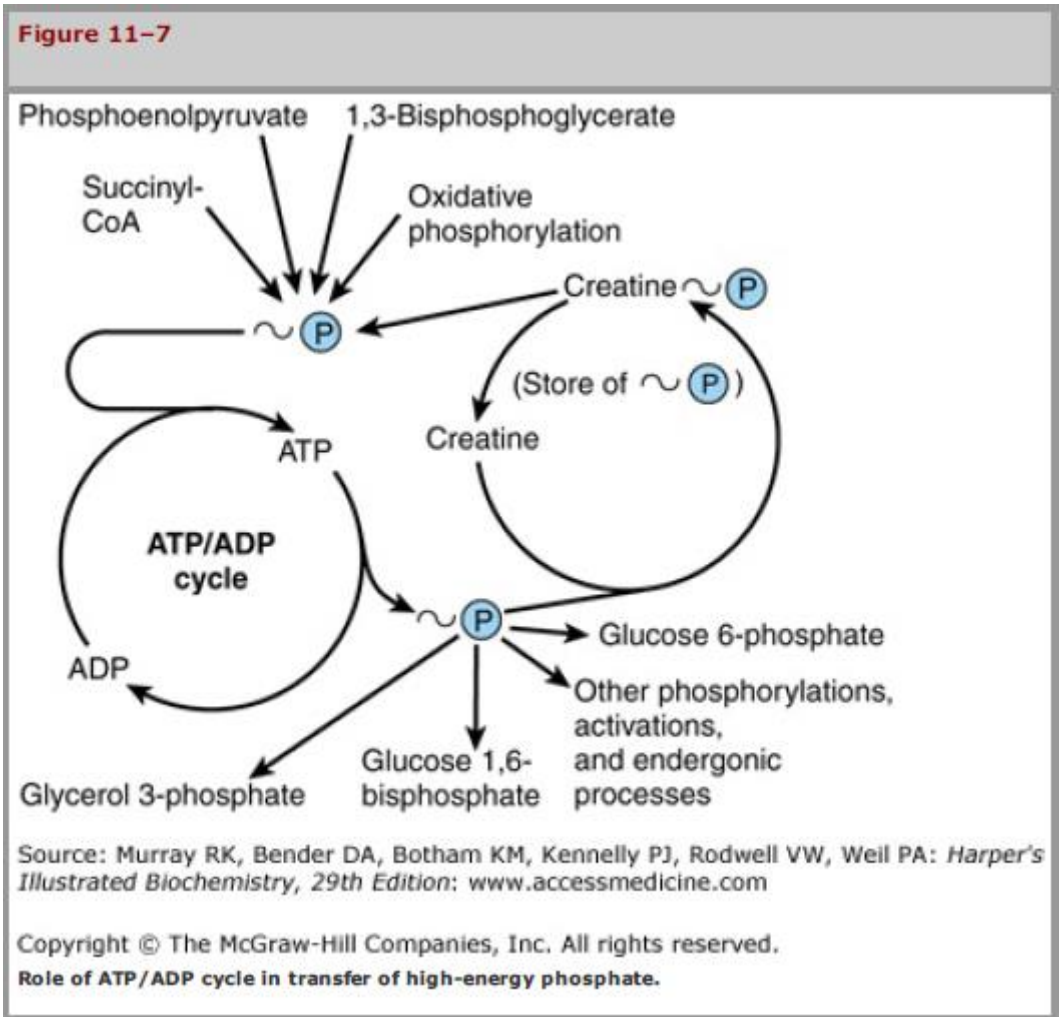


Figure 11-6

HIGH-ENERGY PHOSPHATES ACT AS THE "ENERGY CURRENCY" OF THE CELL

ATP is able to act as a donor of high-energy phosphate to form those compounds below it in **Table 11–1**. Likewise, with the necessary enzymes, ADP can accept high-energy phosphate to form ATP from those compounds above ATP in the table. In effect, an **ATP/ADP cycle** connects those processes that generate ~Ⓟ to those processes that utilize ~Ⓟ (**Figure 11–7**), continuously consuming and regenerating ATP. This occurs at a very rapid rate since the total ATP/ADP pool is extremely small and sufficient to maintain an active tissue for only a few seconds.



There are three major sources of ~Ⓟ taking part in **energy conservation** or **energy capture:**

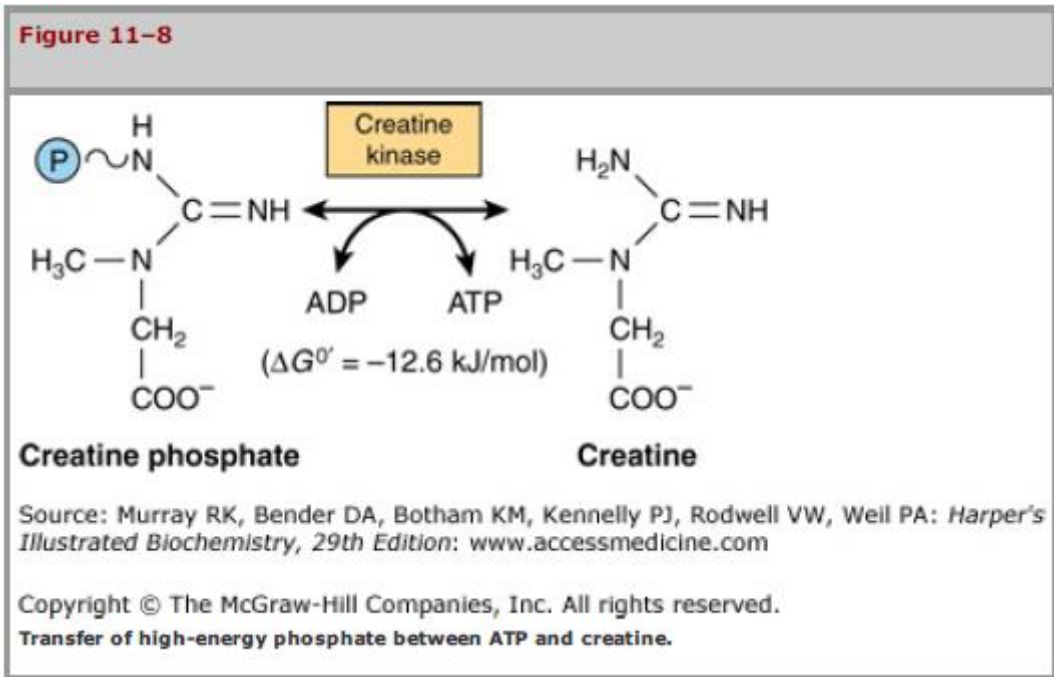
1. **Oxidative phosphorylation.** The greatest quantitative source of ~Ⓟ in aerobic organisms. Free energy comes from respiratory chain oxidation using molecular O2 within mitochondria .

2. **Glycolysis.** A net formation of two ~ results from the formation of lactate from one molecule of glucose, generated in two reactions catalyzed by phosphoglycerate kinase and pyruvate kinase, respectively .

3. **The citric acid cycle.** One ~ is generated directly in the cycle at the succinate thiokinase step .

Phosphagens act as storage forms of high-energy phosphate and include creatine phosphate, which occurs in vertebrate skeletal muscle, heart, spermatozoa, and brain, and arginine phosphate, which occurs in invertebrate muscle. When ATP is rapidly being utilized as a source of energy for muscular contraction, phosphagens

permit its concentrations to be maintained, but when the ATP/ADP ratio is high, their concentration can increase to act as a store of high-energy phosphate (**Figure 11–8**).



ATP Allows the Coupling of Thermodynamically Unfavorable Reactions to Favorable Ones

The phosphorylation of glucose to glucose 6-phosphate, the first reaction of glycolysis (**Figure 18–2**), is highly endergonic and cannot proceed under physiologic conditions:

$$\text{Glucose} + P_i \rightarrow \text{Glucose 6-phosphate} + H_2O \qquad (1)$$
$$(\Delta G^{0'} = +13.8 \text{ kJ/mol})$$

To take place, the reaction must be coupled with another—more exergonic—reaction such as the hydrolysis of the terminal phosphate of ATP.

$$\text{ATP} \rightarrow \text{ADP} + P_i \ (\Delta G^{0'} = -30.5 \text{ kJ/mol}) \qquad (2)$$

When (1) and (2) are coupled in a reaction catalyzed by hexokinase, phosphorylation of glucose readily proceeds in a highly exergonic reaction that

under physiologic conditions is irreversible. Many "activation" reactions follow this pattern.

Adenylyl Kinase (Myokinase) Interconverts Adenine Nucleotides

This enzyme is present in most cells. It catalyzes the following reaction:

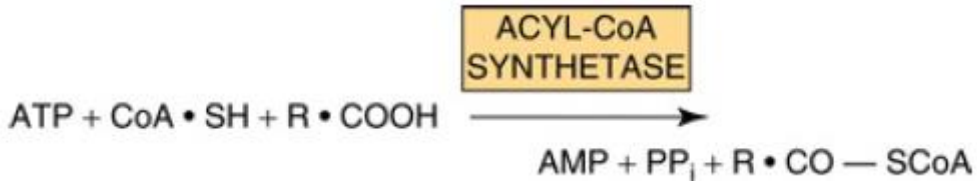
This allows:

1. High-energy phosphate in ADP to be used in the synthesis of ATP.
2. AMP, formed as a consequence of several activating reactions involving ATP, to be recovered by rephosphorylation to ADP.
3. AMP to increase in concentration when ATP becomes depleted and act as a metabolic (allosteric) signal to increase the rate of catabolic reactions, which in turn lead to the

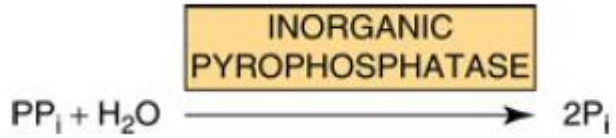
generation of more ATP .

When ATP Forms AMP, Inorganic Pyrophosphate (PPi) Is Produced

ATP can also be hydrolyzed directly to AMP, with the release of PP*i* (**Table 11–1**). This occurs, for example, in the activation of long-chain fatty acids .



This reaction is accompanied by loss of free energy as heat, which ensures that the activation reaction will go to the right and is further aided by the hydrolytic splitting of PP*i*, catalyzed by **inorganic pyrophosphatase,** a reaction that itself has a large *G*0' of –19.2 kJ/mol. Note that activations via the pyrophosphate pathway result in the loss of two ~ rather than one, as occurs when ADP and P*i* are formed.



A combination of the above reactions makes it possible for phosphate to be recycled and the adenine nucleotides to interchange (**Figure 11–9**).

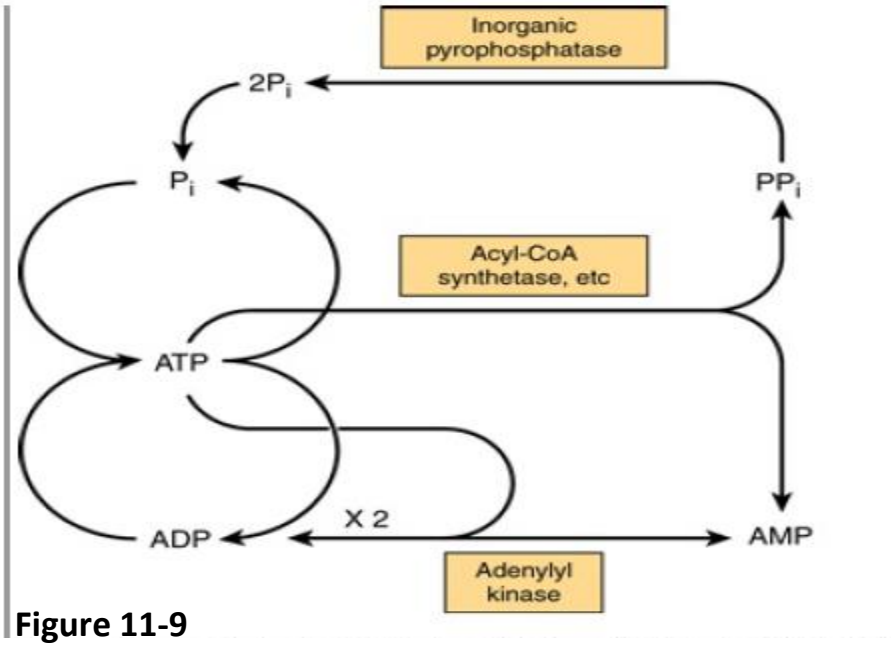
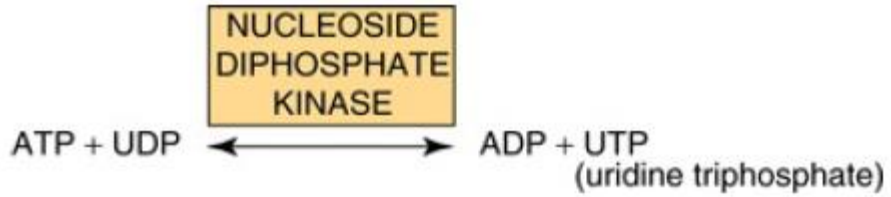


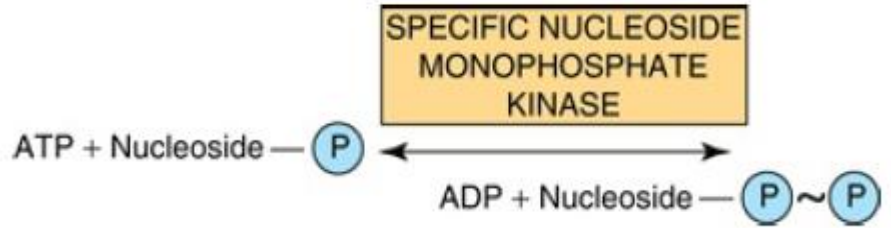
Figure 11-9

Other Nucleoside Triphosphates Participate in the Transfer of High-Energy Phosphate

By means of the enzyme **nucleoside diphosphate kinase,** UTP, GTP, and CTP can be synthesized from their diphosphates, eg, UDP reacts with ATP to form UTP.



All of these triphosphates take part in phosphorylations in the cell. Similarly, specific nucleoside monophosphate kinases catalyze the formation of nucleoside diphosphates from the corresponding monophosphates.



Thus, adenylyl kinase is a specialized monophosphate kinase.