

# Energy Cycle in Vertebrates

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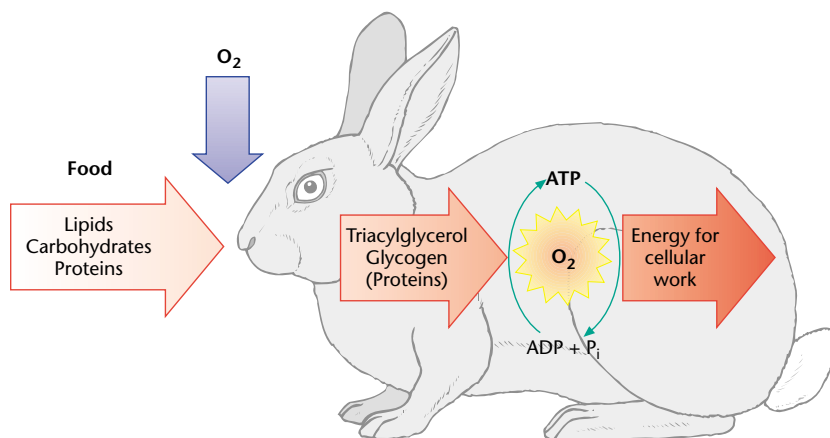
Vertebrates store, mobilize, transport, and use their metabolic fuel reserves to produce ATP, the universal energy currency of all living cells. Depending on the amount of ATP required, the time available to make it and the oxygen availability, ATP synthesis takes place through anaerobic glycolysis or oxidative pathways.

## From Food to ATP

All living organisms use adenosine triphosphate (ATP) as the universal energy currency to support the cellular work necessary for survival and reproduction. However, only small amounts of ATP are available within cells and several metabolic pathways are specifically designed to maintain ATP concentration by replenishing this limited resource at a rate matching its utilization. Animals and humans do not stockpile energy as ATP; instead, they use lipids, carbohydrates and, to a minor extent, proteins for this purpose. These fuel reserves are then progressively broken down to synthesize ATP in synchrony with instantaneous cellular needs. When work must be performed, the required energy can be obtained rapidly by breaking one of the energy-rich phosphate bonds of ATP to produce adenosine diphosphate (ADP) and inorganic phosphate ( $P_i$ ) (see **Figure 1**). How are metabolic fuels stored, mobilized, and ultimately converted to ATP to sustain life processes?

## Energy Reserves

Food enters the body intermittently before being digested and assimilated. The energy not needed instantly is placed in strategic body stores that can be mobilized gradually between meals or during periods of prolonged fasting. For healthy animals feeding normally, over 90% of total fuel reserves are found in lipids, mainly as triacylglycerol in adipose tissue, liver and muscle. Lipids are favoured for long-term ATP synthesis because they can be stored without water and represent the lightest, most concentrated form of biochemical energy. Even if it were possible to store carbohydrates and proteins in anhydrous form, lipids would still yield more than twice as much ATP per gram of fuel. This fundamental advantage is particularly well exploited by migrating birds and hibernating mammals that build lipid depots exceeding half their body weight to power long-distance flight or for overwintering



**Figure 1** Food enters the body as a mixture of lipids, carbohydrates and proteins. These compounds are digested, assimilated and stored as triacylglycerol and glycogen, mainly in adipose tissue, liver and muscle. Over 90% of total energy reserves are in the form of triacylglycerol for long-term, maintenance metabolism. The glycogen reserves are only used when ATP must be produced very quickly or when enough oxygen cannot be supplied to the cells (e.g. during very intensive exercise). When the organism is not eating, the energy contained in triacylglycerol and glycogen is progressively passed on to ATP by the formation of energy-rich phosphate bonds between ADP and  $P_i$ . In turn, the energy needed for cellular work can be harnessed from ATP by the breaking of these phosphate bonds, thereby converting it back to ADP +  $P_i$ . The utilization of metabolic reserves allows for the maintenance of the ADP/ATP cycle that provides all the energy necessary for biochemical work within living cells. Examples of such work are muscle contraction during exercise, pumping of ions across membranes to maintain concentration gradients and the synthesis of macromolecules to make new tissues during growth.

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- ATP synthesis

without eating. In addition to lipids, organisms also keep smaller energy reserves in carbohydrates as glycogen, a polymer of glucose that is mainly stored in liver and muscle. Carbohydrates have the capacity to support much higher maximal rates of ATP production than lipids or proteins and, unlike any other fuel, they can be used in the absence of oxygen. Their unique characteristics make carbohydrates essential for short-term, strenuous work such as moving swiftly to escape a predator, to catch a prey, or in the case of humans, to compete in a 100 m sprint. In addition, some crucial parts of the body such as the nervous system and mammalian red blood cells require glucose as exclusive fuel. Cellular proteins play very important structural (e.g. contractile proteins of muscles) and regulatory roles (e.g. enzymes and ionic pumps), and, therefore, are not normally used to produce ATP. However, extreme circumstances such as extended starvation or long upstream migration in some species of salmon may cause the total depletion of other fuels and lead to the predominant use of proteins, often shortly before death occurs.

## Mobilization and Transport of Metabolic Fuels

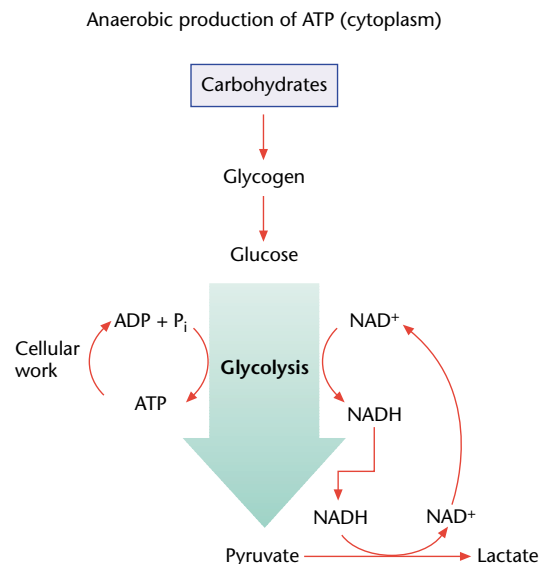
Organisms must be able to mobilize various energy reserves at the appropriate times and rates to meet their life requirements. The building blocks of triacylglycerol and glycogen must be separated before they can be utilized or transported to other tissues. Therefore, fuel mobilization is controlled by complex neural and hormonal mechanisms designed to activate key enzymes that catalyse the hydrolysis of triacylglycerol and glycogen. These specific enzymes are lipases and glycogen phosphorylase. Lipases break down triacylglycerol to fatty acids and glycerol, whereas glycogen phosphorylase cleaves glucose subunits from glycogen. Glucose and long-chain fatty acids can then be further degraded inside the original cells where they were stored, or they can be exported elsewhere by the circulation. For example, exercising mammals provide their locomotory muscles with energy from local sources (muscle triacylglycerol and muscle glycogen reserves) as well as from distant sources (adipose tissue triacylglycerol and liver glycogen). Glucose can be transported easily in blood plasma and through the cytoplasm because it is soluble in these aqueous fluids. However, fatty acids are only lipid-soluble and they must be bound to proteins such as plasma albumin and cytosolic fatty acid-binding proteins to be transported between tissues or within cells.

## ATP synthesis

The selection of a particular substrate or pathway depends on the supply of oxygen, on how fast ATP must be produced, and on fuel availability. Anaerobic glycolysis is the only usable pathway when very high rates of ATP synthesis are required or when enough oxygen cannot be provided. For resting or routine levels of energy expenditure, enough oxygen can be supplied and most of the ATP is produced through energy-efficient oxidative pathways.

## Anaerobic glycolysis

Glycolysis is a cytoplasmic, multienzyme pathway in which the conversion of glucose to 2 pyruvates is accompanied by the net production of 2 ATP and by the reduction of 2  $\text{NAD}^+$  to NADH (NAD = nicotine-adenine dinucleotide). This pathway can only proceed if adequate amounts of  $\text{NAD}^+$  are available. In the absence of oxygen,  $\text{NAD}^+$  is regenerated from NADH through the oxidation of pyruvate to lactate, and the complete pathway that



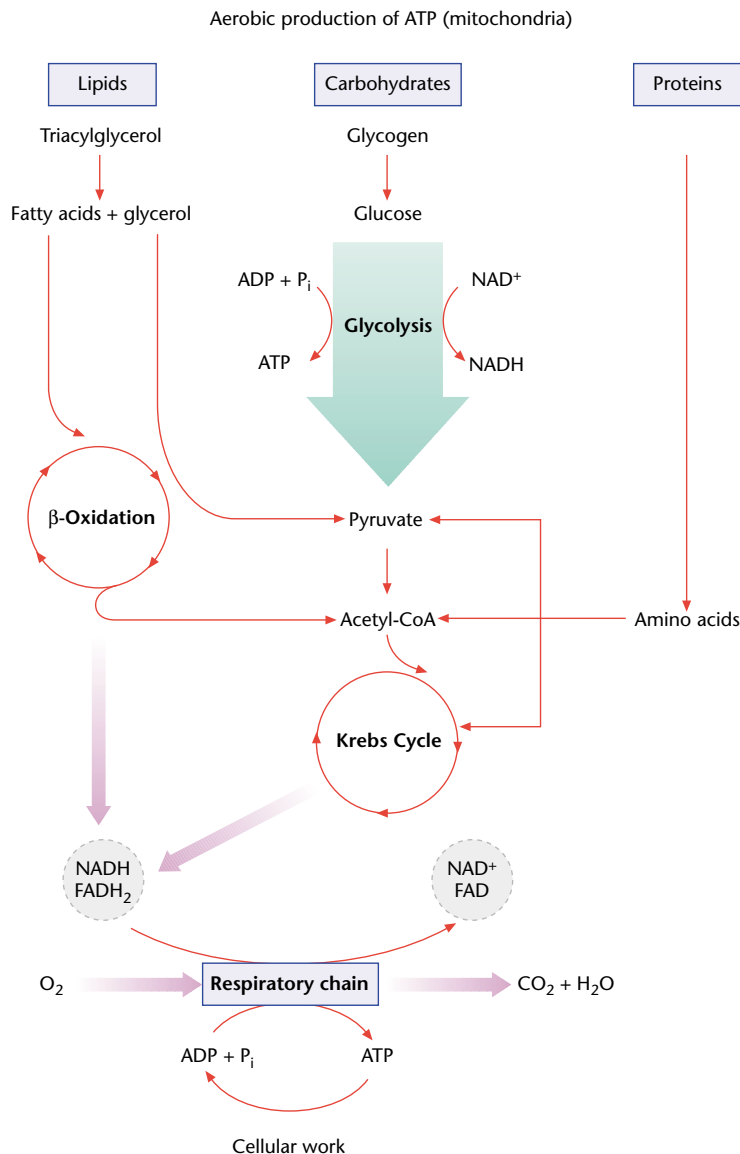
**Figure 2** All cells are capable of producing ATP from carbohydrate reserves in the absence of oxygen. The metabolic pathway used for this transfer of energy from carbohydrates to ATP is called glycolysis and it is located in the cytoplasm.  $\text{NAD}^+$  is an essential cofactor of glycolysis because it must be reduced to NADH in the process of ATP synthesis. To avoid running out of  $\text{NAD}^+$ , cells regenerate it by oxidizing NADH back to  $\text{NAD}^+$  in the last reaction of the pathway that converts pyruvate to lactate. The complete pathway of anaerobic glycolysis has two major advantages: (1) it can produce ATP more quickly than any other pathway, and (2) it can do so without oxygen. However, anaerobic glycolysis is particularly inefficient because it only produces 1/18 of the ATP obtainable from the same amount of carbohydrates when complete oxidation to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  can take place. When ATP does not have to be produced quickly and when  $\text{O}_2$  is provided in sufficient amounts, glycolysis is routinely used without its last reaction to feed pyruvate into the Krebs cycle.

converts glucose to lactate is therefore called anaerobic glycolysis (Figure 2).

## Oxidative pathways

When oxygen is available, NADH is converted back to  $\text{NAD}^+$  by the respiratory chain, or electron transport chain, located in organelles called mitochondria (Figure 3).

There, the complete oxidation of glucose to  $\text{CO}_2$  can take place and it allows the harvesting of large amounts of energy still contained in pyruvate. Mitochondria are often called the power plants of cells because they produce most of the ATP. These organelles possess outer and inner membranes that delimit two compartments, the intermembrane space and the mitochondrial matrix. In the matrix, 2-carbon subunits of acetyl-coenzyme A (acetyl-CoA) are



**Figure 3** ATP can only be produced efficiently through the complete oxidation of metabolic fuels in the presence of oxygen. The enzymes necessary for the oxidation of lipids and carbohydrates to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  are located in specialized organelles called mitochondria. Fatty acids derived from triacylglycerol are broken down to acetyl-CoA by a mitochondrial pathway called  $\beta$ -oxidation. Glycolysis catabolizes glycogen to pyruvate before converting it to acetyl-CoA. Proteins are broken down to individual amino acids that enter the oxidation pathways as pyruvate or acetyl-CoA or directly as intermediates of the Krebs cycle.  $\beta$ -Oxidation, glycolysis and the Krebs cycle produce the energy-rich intermediates NADH and  $\text{FADH}_2$ . The synthesis of ATP from ADP and  $\text{P}_i$  is then coupled to the oxidation of these intermediates by oxygen to  $\text{NAD}^+$  and FAD. The complex pathway allowing the transfer of energy from NADH and  $\text{FADH}_2$  to ATP is called the respiratory chain and it is located in the inner membrane of mitochondria.

sequentially cleaved from long-chain fatty acids through a circular pathway called  $\beta$ -oxidation, and the pyruvate produced by glycolysis is also oxidized to acetyl-CoA. Then, acetyl-CoA is metabolized through the reactions of the Krebs cycle. This cycle is also located in the mitochondrial matrix and it consists of a series of eight enzymatic reactions that lead to the production of 3 NADH and 1 FADH<sub>2</sub> (two energy-rich compounds; FAD = flavin-adenine dinucleotide) from each acetyl-CoA when it is oxidized to CO<sub>2</sub>. These energy-rich intermediates are oxidized back to NAD<sup>+</sup> and FAD by the respiratory chain, a group of electron carriers localized in the inner mitochondrial membrane. The oxidation of each NADH and FADH<sub>2</sub> produces 3 and 2 ATP, respectively, in a process called oxidative phosphorylation. The flow of electrons through the respiratory chain establishes a proton gradient across the inner mitochondrial membrane as they are being pumped from the matrix to the intermembrane space. Protons diffuse back to the matrix through a protein called ATP synthase, thereby stimulating this enzyme to produce ATP. This process is

called phosphorylation because it adds an inorganic phosphate to ADP to form ATP. Taken together, all these reactions allow the use of the energy contained in metabolic fuels to produce phosphate bonds capable of releasing this energy when they are hydrolysed. The complete oxidation of each molecule of glucose produces 18 times more ATP (i.e. 36) than the anaerobic conversion of glucose to lactate (only 2 ATP). Therefore, vertebrates always prefer using oxidative pathways whenever oxygen can be provided fast enough to their tissue mitochondria.

### Further Reading

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