NORMAL MYOCARDIAL METABOLISM: FUELING CARDIAC CONTRACTION

Robert G. Weiss, MD,* and Mikhail Maslov, PhD†

ABSTRACT

The heart has the largest metabolic demands per gram of any organ in the body. Adequate amounts of chemical fuel, namely adenosine triphosphate (ATP), must be generated to support the heart's contractile demands and maintain viability. Fatty acids, ketone bodies, and carbohydrates are the primary substrates of the heart metabolized to generate ATP. Optimal cardiac function depends on the efficient matching of energy generation pathways to energy expenditure. This balance requires the close communication and regulation of various metabolic pathways. Fatty acids are the major source of acetyl coenzyme A for the Krebs cycle and of the oxidative production of ATP. Glycolysis converts glucose to pyruvate and provides a relatively small amount of ATP to the normal adult heart. An understanding of the integration of cardiac metabolism in the well-oxygenated state is important in appreciating deranged cardiac metabolism observed in pathologic states, such as cardiac ischemia and heart failure.

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*Professor of Medicine, Cardiology Division, Johns Hopkins University School of Medicine, Baltimore, Maryland.

†Research Fellow, Cardiology Division, Department of Medicine and MRI Research Division, Department of Radiology, Johns Hopkins Hospital, Baltimore, Maryland.

Address correspondence to: Robert G. Weiss, MD, Johns Hopkins Hospital, 600 North Wolfe Street, Carnegie 584, Baltimore, MD 21287. Email: rweiss@jhmi.edu.

The metabolic demands of the heart are the largest of any organ in the body, and normal cardiac metabolism is required to fuel contractile function and viability. The energy demands of the heart are dependent upon adequate oxygenation and available substrates to generate sufficient quantities of adenosine triphosphate (ATP). ATP is in turn utilized primarily for contraction but also, to a lesser degree, for ionic homeostasis. ATP is produced at high rates to meet myocardial demands. Far more than the total amount of ATP in the myocyte is consumed in less than 1 minute; therefore, the pathways involved in the synthesis of ATP are closely linked to those of ATP utilization in order to quickly respond to changes in energy demand. This article reviews the substrates that are responsible for providing chemical energy in myocytes, the metabolic pathways that convert carbon substrates into those energy-containing metabolites, and current methods for studying human cardiac metabolism.

MYOCARDIAL ENERGY METABOLITES

In the heart, chemical energy is primarily stored in the phosphoryl bonds of metabolites, such as ATP. The concept that a common chemical form of energy, such as that provided by the phosphoryl bonds, could meet divergent energy needs arose decades ago.[1,2] The high-energy phosphate bonds have been likened to electricity in a house that powers many different appliances or to "currency" used to meet many different needs.[1,2] ATP is the most important high-energy phosphate in nearly all cells, including myocytes. It is absolutely required for normal myocardial contractile function and viability.

The most common sites of ATP utilization in myocytes are shown in the Figure. In cardiomyocytes, ATP is mostly used by myofibrillar actin-myosin ATPase to fuel contraction and relaxation processes. ATP is also consumed by Ca^{2+} ATPase in the sarcoplasmatic reticulum to support Ca^{2+} reuptake and by sarcolemmal Na^+/K^+ ATPase to maintain membrane potential, as well as by anabolic reactions and by signaling systems.[3]

Creatine phosphate (PCr) is the other major high-energy phosphate in the heart. PCr is twice as abundant as ATP and serves as a source of ATP through the rapid and readily reversible creatine kinase reaction:

$$\text{creatine phosphate} + \text{ADP} + H^+ \rightleftarrows \text{creatine} + \text{ATP}$$

During ischemia, PCr levels fall rapidly to preserve ATP levels.[4-6] The creatine kinase reaction serves as a temporal buffer to maintain high ATP and low adenosine diphosphate (ADP). The creatine kinase reaction may also serve as a spatial buffer aiding in the intracellular transfer of high-energy phosphates from the sites of generation to the sites of utilization; there are separate mitochondrial and cytoplasmic forms of the enzyme (Figure), and creatine and creatine phosphate diffuse more rapidly than ADP and ATP.[7,8]

Although the concentrations of the high-energy phosphates are higher in muscle than in many organs, the levels are still small relative to the rates of myocardial ATP utilization. For example, the cardiac ATP stores would be depleted in less than 15 seconds if ATP synthesis stopped and utilization rates were unchanged. Thus, the rates of myocardial ATP production and utilization must be closely matched to maintain constant ATP levels.

Metabolic Pathways for Generating ATP in the Normal Heart

Because the chemical energy demands of the heart are so high and the energy stores are relatively limited, myocytes are capable of using a variety of substrates to generate ATP and they contain large numbers of the organelle responsible for most of the ATP generation, the mitochondrion. There are fundamentally 2 mechanisms for ATP synthesis: substrate phosphorylation and oxidative phosphorylation. Oxidative phosphorylation accounts for more than 95% of the ATP synthesized in the heart and occurs in the mitochondria.

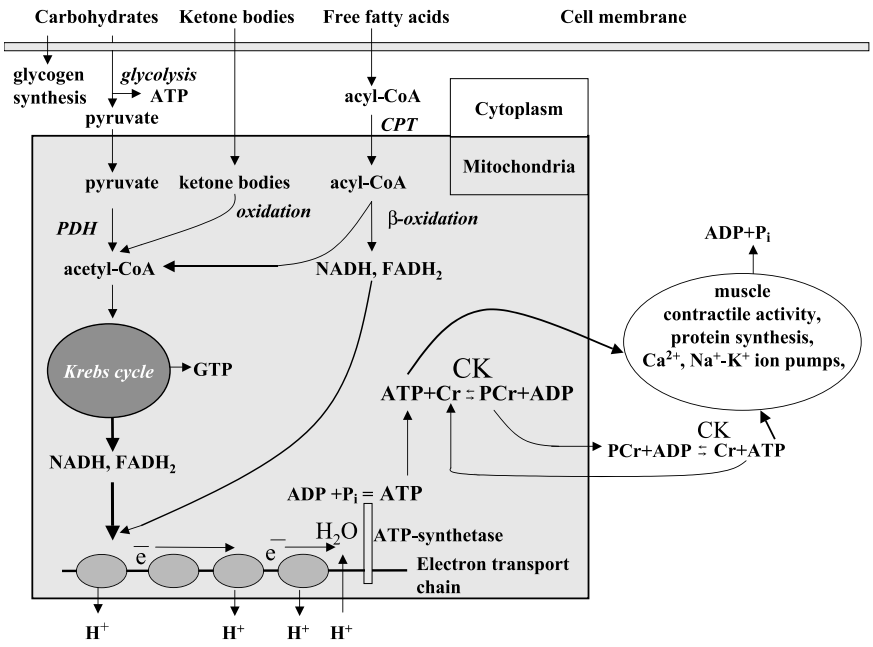
Substrates for ATP Synthesis

There are 3 main types of carbon substrates for myocardial ATP synthesis: fatty acids, carbohydrates, and ketone bodies (Figure). The major pathways for their metabolism are described below.

Fatty Acid Beta-oxidation

Fatty acids are the predominant substrate used in the heart and generate the most ATP. Following uptake of free fatty acids from plasma with specific sarcolemmal fatty acid transport proteins, they are

Figure. Normal Myocardial Metabolism



ATP = adenosine triphosphate; acetyl-CoA = acetyl coenzyme A; PDH = pyruvate dehydrogenase; NADH = nicotinamide adenine dinucleotide; $FADH_2$ = flavin adenine dinucleotide; GTP = guanosine triphosphate; CK = creatine kinase; PCr = creatine phosphate; ADP = adenosine diphosphate; P_i = inorganic phosphate.

activated by fatty acetyl coenzyme A (acetyl-CoA) synthetase and esterified with coenzyme A to form fatty acetyl-CoA, which is soluble. After permeation into mitochondria, fatty acetyl-CoA condenses with carnitine to form acylcarnitine and regenerates fatty acetyl-CoA, which enters beta-oxidation. Fatty acid beta-oxidation takes place in the mitochondrial matrix and produces acetyl-CoA that can enter the Krebs cycle, and nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) that can enter the electron transport chain. The main regulator of fatty acid beta-oxidation is peroxisome proliferator-activated receptor-α (PPARα), which is a member of the nuclear receptor superfamily. PPARα controls gene transcription as a promotor. These genes affect enzymes for fatty acid beta-oxidation and carbohydrate metabolism that include fatty acid transporters, fatty acid binding protein, acetyl-CoA dehydrogenases, malonyl-CoA decarboxylase, carnitine palmityl transferase (CPT), acetyl-CoA synthase, and pyruvate dehydrogenase kinase (PDHK).[9-11] The energy outcome of complete oxidation of 1 mol palmitate is 7 mol $FADH_2$, 7 mol NADH, and 8 mol acetyl-CoA, which ultimately results in approximately 108 mol ATP following Krebs cycle and electron transport metabolism.[12]

Ketone Bodies

Ketone bodies are produced in the liver at times of low blood glucose or during caloric restriction or fasting. They are not metabolized in the liver but in extrahepatic tissues, including muscle. Acetoacetate and 3-hyrdoxybutyrate are common ketone bodies used by the heart. In the heart, ketone bodies are transformed into acetyl-CoA, which enters the citric acid cycle.

Carbohydrate or Glucose Storage and Metabolism

Glucose enters myocytes by means of transport proteins, GLUT 1 and GLUT 4, located in the sarcolemmal membrane and in intracellular microsomal vesicles.[13,14] Myocardial glucose transport depends on the blood glucose concentration and activity of GLUT 1 and GLUT 4; the latter is primarily regulated by insulin. The first step of intracellular glucose metabolism is phosphorylation, after which glucose can either enter glycolysis or be stored as glycogen.

Glycolysis. Only about 4% of myocardial ATP is directly derived from glycolysis.[15] Glycolysis splits a single molecule of glucose into 2 molecules of pyruvate and forms 2 molecules of ATP via substrate-level phosphorylation and 2 molecules of NADH. Despite the relatively small contribution to total ATP during normal conditions, the glycolytic contribution is relatively increased under ischemic or anaerobic conditions, as will be discussed later. Glycolysis is also the primary metabolic pathway for the major carbon substrate store, glycogen (Figure).[16] It has been hypothesized that glycolytically derived ATP may play additional roles by its close location to ion pumps enhancing diastolic relaxation by $Ca2^+$ reuptake into the sarcoplasmic reticulum and for optimal function of the Na^+/K^+ ATPase to maintain an electrochemical gradient.[17,18]

Pyruvate Dehydrogenase Reaction. The pyruvate dehydrogenase (PDH) reaction is a central step feeding the products of glycolysis or lactate directly into acetyl-CoA for entry into the tricarboxylic acid (Krebs) cycle. Regulation of PDH by fatty acids, for example, limits glucose entry into the Krebs cycle and is a critical step regulating myocardial substrate choice and utilization.[19,20] Lactate decarboxylation is another important source of pyruvate for PDH, because lactate produced by other organs and skeletal muscle can be extracted from blood and rapidly oxidized by lactate dehydrogenase into pyruvate. Pyruvate enters mitochondria with H^+ by means of a special transport system located in the inner mitochondrial membrane. PDH activity depends on the activation state of the enzyme, which is inactivated by PDHK and activated by dephosphorylation by PDH phosphatase.[21-23]

Krebs Cycle. The tricarboxylic acid, or Krebs, cycle is a common metabolic pathway where the products of carbohydrate, ketone body, and free fatty acid oxidation are converted into reducing equivalents and carbon dioxide. Acetyl-CoA condenses with oxaloacetic acid, releasing coenzyme A. During a series of linked reactions, the 2 carbons from the acetyl group are released as carbon dioxide, and oxaloacetic acid is regenerated. The result of the Krebs cycle is synthesis of 1 molecule of ATP via substrate phosphorylation and the formation of reducing equivalents, including 3 molecules of NADH and 1 molecule of $FADH_2$ from 1 molecule of acetyl-CoA, which then proceed to the electron transport chain to be oxidized and generate ATP.

Oxidative Phosphorylation

More than 95% of cardiac ATP is generated from oxidative phosphorylation at the electron transport chain in mitochondria. The essence of oxidative phosphorylation is that energy is released from NADH and $FADH_2$ received from the Krebs cycle, by in turn reducing O_2 to O_2^- and creating an H^+ gradient that is coupled to ATP synthesis from ADP and inorganic phosphate (P_i).

Specifically, energy is released from reducing equivalents as electrons move through the electron transport chain and protons move to the outside of the inner mitochondrial membrane to generate a proton gradient for ATP synthase activation. This is accomplished by an enzyme complex of 5 highly specialized proteins that are typically encoded by proper mitochondrial DNA. Electron flux is regulated to maintain a charge gradient across the membrane. The free energy released by the spontaneous diffusion of protons through the channel at the end of the electron transport chain leads to a reaction between the ADP and a free phosphate group, creating an ATP molecule.[12,24] Thus, in mitochondria, redox and phosphorylation reactions are coupled for ATP synthesis, thereby linking the reactions.

Phosphotransfer Networks

In addition to providing a rapid source of ATP and buffering changes in ATP, ADP, and P_i, phosphotransfer networks may also enhance the transfer of energy-rich phosphoryls between the mitochondria and myofilaments. They consist of the creatine kinase and adenylate kinase reactions, and it seems likely that these are multiple-linked reactions.[25]

The creatine kinase reaction has been well studied. ATP is synthesized in mitochondria but has restricted permeability to cytosol and sites of utilization. A PCr shuttle involving mitochondrial and cytosolic forms of creatine kinase has been postulated to enhance the transfer of energy for ATP regeneration in myofilaments and ADP generation in the mitochondria. In mitochondria, this reaction is regulated by mitochondrial creatine kinase; in the cytosol, it is regulated by muscle-type creatine kinase. The creatine kinase reaction serves as the heart's primary energy reserve system, and PCr serves as the prime energy reserve metabolite.[3,5,12,26,27] PCr is first consumed during early ischemia to preserve ATP. Adenylate kinase catalyzes the reversible reaction: 2ADP $\rightarrow$ATP+adenosine monophosphate. Adenylate kinase is implicated in the regulation of ion channels and transporters, especially when creatine kinase is impaired.[25]

Regulation and Interconnection Among Metabolic Pathways

Optimal cardiac function depends on the efficient matching of energy generation to energetic demands and the orchestrated metabolism of multiple substrate oxidation to generate sufficient ATP under varied physiologic conditions. In the actively pumping heart, the rate of ATP hydrolysis must match the rate of ATP resynthesis. The focus in this review has been on the metabolic pathways that generate ATP, but it is clear that the products of ATP utilization, ADP and P_i, regulate ATP utilization and control the free energy that is released when ATP is consumed.[28]

In general, the rates of substrate movement through common pathways are determined as metabolites pass through key steps and are inhibited by reaction products or reducing equivalents, such as ATP, NADH, and $FADH_2$, and are stimulated by ADP, NAD+, and FAD. A key step in fatty acid beta-oxidation is CPT-I, which transports fatty acids into mitochondria. The CPT-I activity is inhibited by malonyl-CoA, which is formed from carboxylation of acetyl-CoA by acetyl-CoA carboxylase.[22,29] The rate of glycolysis is regulated by key enzymes. The activity of phosphofructokinase is inhibited by H^+, citrate, and ATP and is stimulated by ADP, Ca^{2+}, and fructose 2,6-diphosphate.[12,22] A high mitochondrial NADH/NAD^+ ratio depresses the glyceraldehyde 3-phosphate dehydrogenase activity, providing conversion of glyceraldehyde 3-phosphate to 1,3-diphosphoglycerate.[30-32] PDH is controlled by PDHK and PDH phosphatase enzymes; PDHK enzymes inhibit, and PDH phosphatase enzymes stimulate, pyruvate decarboxylation.[21,22] The activity of PDH kinase in turn is inhibited by pyruvate and ADP and activated by the high ratios of acetyl-CoA/CoA and NADH/NAD^+, and PDH phosphatase activity is increased by Ca^{2+} and Mg^{2+}.[23]

Fatty acid and glucose metabolism meet at the Krebs cycle, fueling it with acetyl-CoA. Cytosolic malonyl-CoA concentrations maintain the reciprocal reg-

ulation of pyruvate and free fatty acid metabolism.[32-34] A high rate of fatty acid beta-oxidation results in an increase in content of the NADH/NAD^+ and acetyl-CoA/CoA in the mitochondrial matrix that activates PDHK and leads to less glucose and lactate oxidation.[32,35] The main point is that myocardial energy metabolism is extremely complex and redundant, allowing for close regulation of chemical energy formation and sustained generation during times of altered demand and substrate availability.

Models of Cardiac Metabolism

Both mathematical and computational models have been used to study the mechanisms of energy metabolism.[36] Three basic classes of models used to investigate metabolic processes include enzymatic, lumped, and kinetic models. Enzymatic models are used to describe in detail the behavior of key regulatory enzymes in related pathways. The lumped models provide insight by grouping reactions into one process. Lastly, the kinetic models describe each of the reactions involved in a metabolic pathway and may include regulation of each enzyme involved. Another class of models that have provided insight into glycolysis, palmitate oxidation, the Krebs cycle, and oxidative phosphorylation are hybrid models that include multiple components of respiration in one model.[37] The combination of detailed models, including incorporation of enzymes into different stages of the cycle being studied, have provided some unique insights into cardiac energy metabolism that cannot be obtained from conventional experimentation alone.

Human Myocardial Metabolism

It has been historically difficult to study human cardiac metabolism under physiologic conditions. Our original understanding of human myocardial substrate utilization arose primarily from studies in which samples of arterial and coronary sinus blood were analyzed for substrate content and uptake.[38] In addition, myocardial specimens obtained at biopsy or during surgery provided the initial insights into the abundance of key metabolites, such as ATP.[5,39] In the past decade, noninvasive imaging techniques have provided additional insights into myocardial substrate uptake and high-energy phosphate content. Positron emission tomography has been used to assess myocardial glucose uptake, fatty acid oxidation, and Krebs cycle flux.[40-42] Nuclear magnetic resonance spectroscopy has been used as a noninvasive method to quantify myocardial ATP and creatine phosphate concentrations, as well as calculated free ADP.[43-45] These techniques have provided important insights in the metabolic causes and consequences of common clinical conditions such as ischemia,[6,46] viability,[40] and heart failure.[47]

Conclusion

The well-oxygenated heart consumes several different substrates and converts them to a common form of chemical energy that fuels myocardial contraction and is required for viability. The interactions and mechanisms controlling myocellular respiration have been studied in animal models and in people. Cardiac metabolism is primarily aerobic, and most of the energy (ATP) is supplied via oxidative phosphorylation. An understanding of cardiac metabolism in the well-oxygenated state is critical for appreciating the causes and consequences of deranged cardiac metabolism in pathologic states, such as cardiac ischemia and heart failure.

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