THE ROLE OF FATTY ACID OXIDATION IN CARDIAC ISCHEMIA AND REPERFUSION

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exact mechanisms involved in the control of cellular respiration have been debated, the direct relationship between oxygen consumption and cardiac work has been well documented.

Cardiac metabolism is primarily aerobic and most of the energy (ATP) is supplied via oxidative phosphorylation. During a mild ischemic episode (such as during an anginal attack), oxidative metabolism decreases in proportion to the decrease in oxygen supply, although fatty acid oxidation remains the primary source of residual metabolism. Nonetheless, the production of ATP via glycolysis increases during ischemia. Anaerobic glycolysis may be able to maintain contractility but cellular integrity is sacrificed due to increased tissue concentrations of lactate and hydrogen ions. The following review provides an overview of the role of fatty acid oxidation in cardiac ischemia and reperfusion.

**Metabolic Homeostasis**

Cells in the heart are able to rapidly alter overall energy input and output in relationship to energy demands. Dramatic changes in energy demands are met while maintaining a near constant level of metabolites in the cytoplasm and mitochondria. The mechanics responsible for this equilibrium have been studied for decades and it is still a somewhat controversial issue. Once thought to be due to a simple feedback loop, it is now accepted that the orchestration of this remarkably rapid flux of metabolites and energy is controlled by a much more complex systems and involves a "metabolic homeostasis" of metabolites used for energy consumption in the cytoplasm. Such equilibrium exists over a range of workloads and is thought to be controlled by a complex cytoplasmic and mitochondrial network that regulates the rate of ATP production. The heart’s ability to maintain this balance of energy metabolism and output is compromised when a condition that impairs cardiac energy metabolism exists, such as in the case of ischemia.

**Increase in Fatty Acid Levels Following an Acute Event**

In order to meet energy requirements, the heart regulates the production of acetyl-CoA. Acetyl-CoA is a substrate used in the tricarboxylic acid cycle (Krebs cycle) in the generation of ATP. The beta oxidation of fatty acids is a major source of acetyl-CoA. In the ischemic state (during angina, after acute myocardial infarction, or during cardiac surgery), the circulating levels of fatty acids increase. Fatty acids are hydrophobic and depend upon a complex process for transport across the mitochondrial membrane (Figure 1). The first compound required for this process is carnitine. Carnitine makes the transport of long-chain fatty acids through the inner mitochondrial membrane possible. Carnitine palmitoyltransferase is an enzyme that, in the presence of carnitine, transfers fatty acyl groups from acyl CoA to carnitine thereby forming acyl carnitine. The acyl carnitine is then able to enter the mitochondrial matrix, where it is converted back to acyl CoA and enters the fatty acid beta oxidative pathway to produce acetyl-CoA.

Another compound critical in the regulation of fatty acid transport is malonyl CoA. Malonyl CoA is an important endogenous inhibitor of fatty acid oxidation and acts in opposition to carnitine. Simplistically speaking, carnitine acts to increase fatty acids available for beta oxidation while malonyl CoA acts to decrease it. The enzyme involved in the synthesis of malonyl CoA is acetyl-CoA carboxylase (ACC), which is in turn regulated by adenosine monophosphate (AMP)-activated protein kinase (AMPK). A third enzyme, malonyl CoA decarboxylase, acts to convert malonyl CoA back to acetyl-CoA.
METABOLIC CHANGES IN ISCHEMIA AND REPERFUSION

Although we know that the metabolic pathways during ischemia and reperfusion of the heart are drastically altered, the exact molecular mechanisms essential to these changes have not been fully delineated. It has been suggested that AMPK has a pivotal role in the mediation of fatty acid and glucose metabolism and has even been called “a metabolic master switch.” Restrictions in oxygen supply to the cardiac tissue result in a decrease in both fatty acid and glucose oxidation. During ischemia, AMP accumulates and in turn stimulates AMPK (Figure 2). ACC is phosphorylated by AMPK resulting in a decrease in ACC activity and decreased synthesis of malonyl CoA. This decrease in the synthesis of malonyl CoA is coupled with the maintenance of malonyl CoA degradation by malonyl CoA decarboxylase, the consequence of which is a dramatic decrease in malonyl CoA levels during reperfusion of ischemic hearts. The end result is a loss in the control of mitochondrial fatty acid uptake and increased levels of fatty acids available for oxidation.

Human and animal models of cardiac ischemia have demonstrated that after myocardial ischemia and reperfusion, the rate of fatty acid oxidation in the heart increases rapidly and meets or exceeds preischemic rates. These high rates of fatty acid consumption after ischemia and reperfusion are associated with an increase in oxygen consumption and a net loss of cardiac efficiency. Thus, high plasma fatty acid concentration and alterations in the control mitochondrial fatty acid uptake result in an increased severity of ischemic damage. As a result, the reduction, not increase, of fatty acids available after reperfusion is associated with an improvement in recovery.

**COMPARISON OF FATTY ACID AND GLUCOSE METABOLISM**

**EFFECTS ON ATP PRODUCTION AND IONIC HOMEOSTASIS**

The metabolic pathway for fatty acids and glucose in the heart under aerobic conditions is shown in Figure 3. As previously mentioned, the heart derives most of its energy from the oxidation of fatty acids over the use of carbohydrates; however, fatty acid oxidation consumes about 10% more oxygen than required by glucose metabolism to produce the same amount of ATP. ATP produced by fatty acid metabolism or glucose oxidation is dependent on the presence of oxygen. On the other hand, ATP produced via glycolysis is not oxygen dependent. These factors contribute to making fatty acids less efficient than glucose as a source of energy regarding consumption of oxygen.

Ischemia of the myocardium results in dramatic alteration of fuel metabolism and the effects of ischemia on fatty acid metabolism are shown in Figure 2. Low levels of oxygen during ischemia alter the normal oxidative processes for production of ATP shifting more importance to glycolysis as a source of ATP. However, pyruvate generated from glycolysis is converted to lactate...
rather than being completely metabolized to CO2 and H2O in the mitochondria.15,19-21 The resultant increased production of lactate and protons in the setting of ischemia results in a decrease in contractile work and a dramatic disruption in cellular homeostasis.19,20

Changes in ionic homeostasis in the cell, such as high levels of cytosolic calcium, result from the impaired generation of ATP during ischemia.22 The sarcoplasmic reticulum is unable to take up calcium at normal rates in the setting of decreased ATP. The resultant increase in cytoplasmic calcium has 4 primary metabolic consequences for the heart: (1) ischemic contracture is promoted resulting in a further fall in the already low ischemic blood flow, (2) calcium overload of the mitochondria promotes the depletion of ATP; (3) some phospholipases are activated and thereby assist in the destruction of cell membranes and accumulation of harmful detergent lysolcithins, and (4) the stage is set for a predisposition to calcium-mediated arrhythmias.

**EXACERBATION OF MYOCYTE NECROSIS**

During aerobic conditions, the mitochondria produce large amounts of ATP.23 During anaerobic conditions, the integrity of the mitochondrial membrane begins to break down as production of ATP is reduced. A simplistic view of cell death in ischemia involves the concept of a critical level of ATP required for life and suggests that once levels of ATP drop below this level, vital functions cease, and all is lost.1 Although a reduction in ATP is a sign of metabolic deterioration and poor prognosis, myocyte death in ischemia is not this simple. Rather, cardiac cell death involves not only necrosis but also apoptosis, which is not dependent on ATP depletion. A key component of this process is the release of cytochrome C from mitochondria damaged due to a variety of stimuli, one of which is ischemia.

Mitochondria are vital mediators of myocyte damage during ischemia and reperfusion.24 Functional and ultrastructural mitochondrial injury occurs early in the course of ischemia and damage progresses as the duration of ischemia increases. After 10 to 20 minutes of severe ischemia, the mitochondrial oxidative function and cardiac contractile function are able to recover. If ischemia is sustained for longer periods, such as for 30 to 45 minutes, irreversible myocyte damage begins due to irreversible defects to the distal electron transport chain. The result is myocyte death.

**MECHANISMS OF DIMINISHED CARDIAC EFFICIENCY**

Profound metabolic sequelae result from ischemia making the unbalanced utilization of fatty acids and carbohydrates even more important in the poorly oxygenated heart. High levels of fatty acids following an ischemic event have detrimental effects on the mechanical and electrophysiologic characteristics of the heart after reperfusion. The excessive production of protons in the heart due to glycolysis can result in accumulation of sodium and calcium ions. This overload in calcium may contribute to reperfusion injury by inducing excessive myofilament activation at the time of re-oxygenation and by causing an increase in mitochondrial calcium.25,26

When mitochondrial calcium levels increase, the ability to generate ATP is subsequently decreased limiting the metabolic recovery of the myocyte. Lastly, calcium-activated proteases can act to destroy critical intracellular structures.25,27 During reperfusion, the heart is a relatively inefficient pump as it is required to spend much of the limited ATP on re-establishing a normal intracellular pH and not on contractility.1 High fatty acid oxidation rates exacerbate this inefficiency, primarily by inhibiting glucose oxidation.5,18

**CONCLUSIONS**

The well-oxygenated heart consumes substrates to produce power and heat. The metabolism of fatty acids is important as a source of ATP and accounts for 50% to 70% of the total energy required for cardiac function while much of the rest is generated from carbohydrates via glucose oxidation and glycolysis. Levels of fatty acids increase dramatically during and following ischemia. This combined with alterations in intracellular control of fatty acid oxidation keep fatty acids the predominant fuel during and following ischemia. This high fatty acid oxidation inhibits glucose oxidation contributing to the excess production of lactate and protons. Consequently, ionic homeostasis is eventually disrupted resulting in myocyte necrosis and decreased cardiac efficiency.

Ischemic heart disease is a metabolic problem. Manipulation of cardiac metabolism may hasten functional recovery from ischemic events. Therapies aimed towards direct or indirect stimulation of myocardial glucose metabolism, a more oxygen-efficient form of ATP production than fatty acid oxidation, provide promise for the treatment of ischemic heart disease.
REFERENCES


