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The role of cardiac energy metabolism in cardiac hypertrophy and failure

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ABSTRACT

In mammalian heart, incessant production of cellular energy is vital for maintaining continuous mechanical pumping function providing the body for oxygen and nutrients. To ensure this essential function, cardiac muscle adapt to increased energy demand or compromised energy supply by reprogramming the network of genes whose products are necessary to match the production of energy to consumption. Failure in this regulation leads to severe cardiac dysfunction and has been associated with cardiac pathogenesis including cardiac hypertrophy, failure and diabetes. Metabolic adaptations are induced by network of transcriptional pathways that are activated by a variety of factors such as hormones, nutrients, second messengers and oxygen. The metabolic phenotype of the heart is maintained by pathways controlling transcriptional regulators, which include peroxisome proliferator-activated receptors, estrogen-related receptors and nuclear respiratory factors, as well as their common coactivator protein peroxisome proliferator-activated receptor γ coactivator 1. These central regulators of gene expression are complemented with factors such as hypoxia inducible factor 1, which is activated in insufficient oxygenation of the tissue. Here, we discuss how these pathways relate to the cardiac metabolism and how they interact with pathways controlling the contractile phenotype of the heart.

1. Introduction

The mechanical pumping function of the heart provides sufficient and constant flow of oxygen and nutrients to itself and other tissues in the mammalian body. To secure the availability of energy substrates, heart has developed into a “multifuel” organ able to use fatty acids, glucose, lactate, amino acids and ketone bodies as a source of energy. In a healthy heart, production of cellular energy (ATP) in cardiac muscle cells relies heavily on mitochondrial oxidative phosphorylation fuelled mainly by fatty acid oxidation and to lesser extent on glucose oxidation or glycolysis. Cardiac metabolism has wide adaptive capacity and plasticity when facing conditions that challenge heart energy production. However, most forms of cardiac diseases are associated with maladaptive changes in energy metabolism exacerbating the disease progression. Development of pathological hypertrophy and concomitant heart failure are associated with reduced contractile function in parallel with shift in energy substrate preference from fatty acids to glucose and gradual decline of mitochondrial oxidative phosphorylation. Here we discuss how cardiac energy metabolism and maladaptive metabolic alterations are associated with cardiac disease. Further, we highlight some of the mechanisms and transcriptional pathways linking hypertrophy and contractile function to energy metabolism in the development of heart failure.

2. Sources and sinks of cardiac energy

In the mammalian embryo, proliferating cardiomyocyte precursor cells are dependent on glycolysis as a source of energy, while mitochondrial organization and oxidative metabolism are poorly developed [1]. Although the heart develops in a low oxygen environment and high rates of glycolysis and lactate production are typical, fetal hearts are still able to oxidise lactate and fatty acids. However, oxidation contributes only a minor fraction of the total ATP production (~15%) [2]. As cardiomyocytes differentiate more towards the adult phenotype, there is a switch from glycolytic metabolism towards mitochondrial oxidative phosphorylation [1]. During the neonatal period β-oxidation increases, which is accompanied by a parallel decrease in glycolytic rates. Eventually, adult heart muscle gets ~90% of its energy from oxidative phosphorylation. Mitochondria occupy ~30% of cardiomyocyte volume and there is direct correlation between

Abbreviations: CoA, coenzyme A; TCA, tricarboxylic acid; $[Ca^{2+}]_i$, cytosolic free Ca^{2+}; E-C, excitation-contraction; SR, sarcoplasmic reticulum; SERCA, SR Ca^{2+}-ATPase; AMPK, adenosine monophosphate-activated protein kinase; MEF2, myocyte enhancer factor-2; PPAR, peroxisome proliferator-activated receptor; ERR, estrogen-related receptor; NRF, nuclear respiratory factor; PGC-1, peroxisome proliferator-activated receptor γ coactivator 1; TFAM, mitochondrial transcription factor A; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; HIF-1, hypoxia-inducible factor 1; ROS, reactive oxygen species; CaMK, calcium/calmodulin-dependent kinase; p38 MAPK, p38 mitogen activated protein kinase; CREB, cyclic nucleotide regulatory element binding protein

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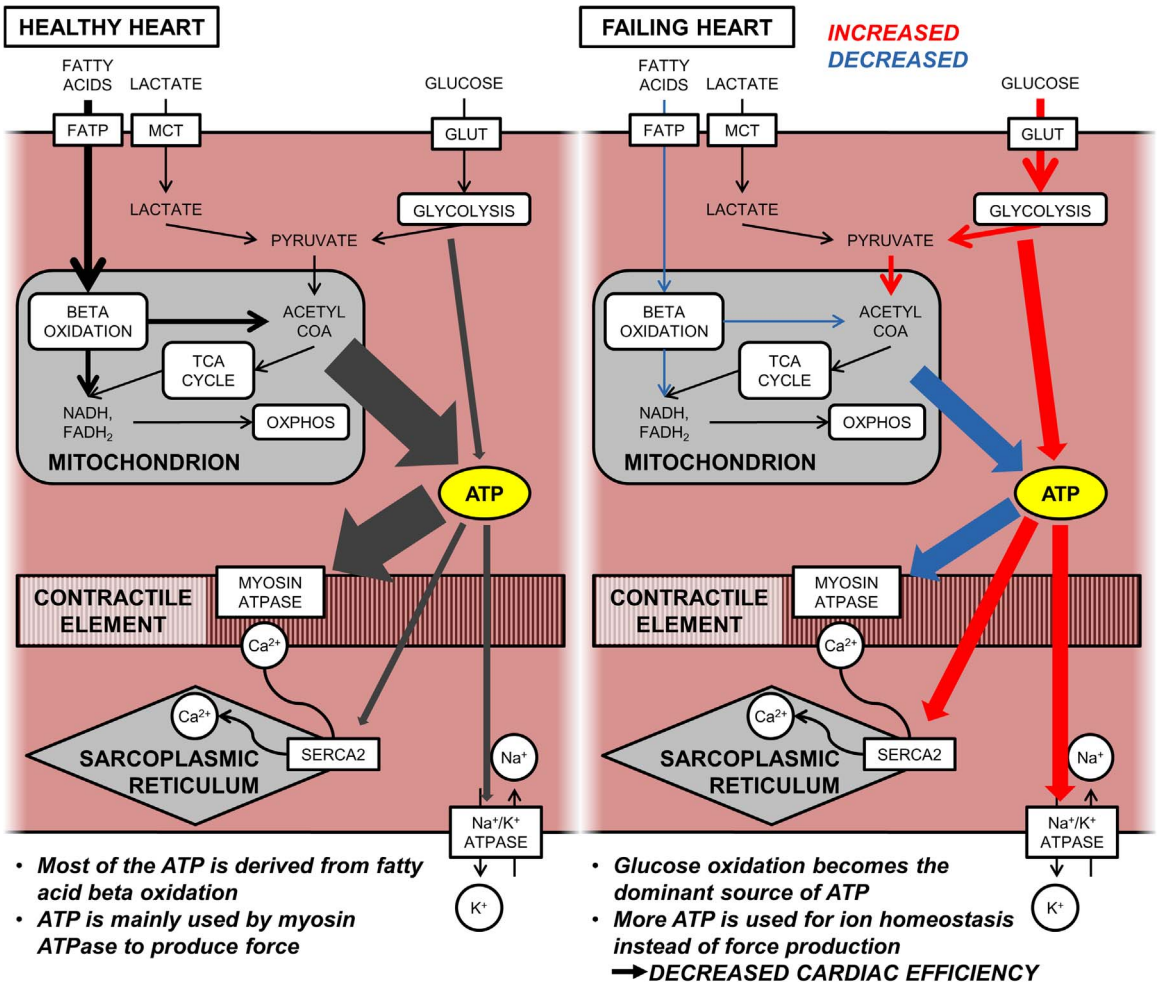

Fig. 1. Energy production and expenditure in cardiomyocytes of healthy and failing heart. Normally, most of the cardiomyocyte ATP is produced via oxidation of fatty acids and consumed mainly by myosin ATPase in the contractile machinery to produce the force of heart contraction. In failing heart, metabolic phenotype shifts towards the use of glucose oxidation. At the same time changes in ion homeostasis reduce the cardiac efficiency, which together with the impairments in energy production leads to insufficient force production. *FATP, fatty acid transporter; MCT, monocarboxylate transporter; GLUT, glucose transporter; OXPHOS, oxidative phosphorylation.*

cardiac workload and oxygen consumption [3,4].

The heart produces energy from the oxidation of fatty acids, glucose and lactate, and to a lesser extent from ketone bodies and amino acids (Fig. 1). Fatty acids are covalently bound to coenzyme A (CoA) to form fatty acyl-CoA in the cytosol and transported into mitochondria via the system composed of carnitine palmitoyltransferase and carnitine-acylcarnitine translocase. In the mitochondrion, acyl-CoA enters β-oxidation, where acetyl-CoA and reduced electron carriers (NADH, $FADH_2$) are the main products. Glucose oxidation is a minor but important component of the total cardiac energy production. Under physiological conditions, glucose is transformed to pyruvate, which enters mitochondria and is decarboxylated and bound to CoA by pyruvate dehydrogenase to form acetyl-CoA. Acetyl-CoA from both β-oxidation and pyruvate oxidation enters the tricarboxylic acid (TCA) cycle, resulting in the formation of NADH and $FADH_2$, which feed electrons into the respiratory chain, thus providing the force to create the mitochondrial proton gradient. The electrons that travel down the respiratory chain are eventually transferred to O_2 via cytochrome oxidase and H_2O is formed [4,5]. The large electrochemical proton gradient over the mitochondrial membrane is discharged through the F_1F_0-ATPase, which utilises this force to phosphorylate ADP to ATP. When oxygen availability is not limiting, the main part of cardiac energy comes from the oxidation of fatty acids so that 60–90% of the acetyl-CoA comes from β-oxidation, and 10–40% comes from the oxidation of pyruvate. Pyruvate is derived in approximately equal amounts from glycolysis and lactate oxidation [6].

When the availability of oxygen and nutrients is not limiting, the two important factors regulating the cardiac energy production are the cellular concentrations of ADP and Ca^{2+}(Fig. 2). The rate of respiration is regulated by the availability of ADP to the F_1F_0-ATPase, and thereby the rate of oxidative phosphorylation is linked to the rate of ATP hydrolysis, ensuring that the ATP content remains constant even during large increases in cardiac energy consumption [6]. Cytosolic free Ca^{2+}($[Ca^{2+}]_i$) regulates the activity of the key enzymes of the TCA cycle [5] and because cytosolic Ca^{2+} signals also activate the contraction of the myocyte in a concentration-dependent manner, the function of the myocyte (contraction) and the energy production (TCA cycle) are inherently tightly connected. The process linking the electrical events at the cell membrane and the contraction together via transient elevation of $[Ca^{2+}]_i$ is known as excitation-contraction (E-C) coupling [7], involving a wide variety of proteins located in the cell membrane, cytosol, sarcoplasmic reticulum (SR) and other cell organelles. Altogether the E-C coupling consumes vast amounts of energy and it has been estimated that 2% of the cellular ATP is consumed during each contraction cycle, primarily for contraction but also for ionic homeostasis [4,5]. The main cardiomyocyte energy consumers are the myosin ATPase of the contractile filaments, plasmalemmal Na^+/K^+-ATPase and SR Ca^{2+}-ATPase (SERCA). Approximately 60–70% of ATP goes to contraction, and the remaining 30–40% is primarily used by SERCA and other ion pumps. This highlights the energy cost of active calcium signalling as 15% of cardiac energy expenditure is due to SERCA ATPase activity [6,8].