Signalling in cardiac metabolism

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1. Introduction

The heart requires large amounts of energy to sustain contractile function, and is the major consumer of energy in the body on a weight basis. Energy reserves are limited in the heart, so energy in the form of adenosine triphosphate (ATP) must be produced continually by the catabolism of different energy carbon substrates. The heart is an ‘omnivore’ and can use a number of different energy substrates, including fatty acids, glucose, lactate, pyruvate, ketones, and amino acids.¹–⁴ Myocardial energy metabolism must be tightly regulated, as the heart cannot afford to produce either too little or too much ATP. In the normal healthy heart, almost all (>95%) of the ATP generated in the heart comes from mitochondrial oxidative phosphorylation, with the remainder being derived from glycolysis.¹–⁴ Of these, fatty acids, glucose, and lactate normally make the greatest contribution to overall energy metabolism, primarily because the heart sees the highest concentration of these energy substrates. Mitochondrial metabolism of fatty acids accounts for ~60–90% of the total energy production (in the form of ATP), with carbohydrates contributing the remaining 10–40%.³ The contribution of fatty acids and carbohydrates to oxidative ATP production in the heart is influenced by a number of conditions, including alterations in hormonal control, workload, energy substrate supply, and oxygen supply to the heart. The control of these energy-producing pathways is complex, but the different pathways normally work in perfect harmony to ensure the energy needs of the myocardium are met. The energy homeostasis mechanisms of the heart maintain constant ATP production despite periods of dramatic shifts in workload to the heart, and changes in energy substrate and/or oxygen supply to the heart. A complex and integrated cardiac signalling pathway has evolved to allow a precise match between cardiac energy production and usage. This Spotlight issue of Cardiovascular Research addresses some of the complex signalling pathways involved in the physiological control of energy metabolism in the heart. Dysregulation of cardiac metabolic pathways relevant to common diseases that leads to heart failure is also addressed.

2. Control of myocardial mitochondrial function

As mentioned, mitochondrial oxidative metabolism is the major source of ATP production in the heart. It is now well established that alterations in mitochondrial function contribute to the pathogenesis of heart failure, including ischaemic heart disease, diabetic cardiac dysfunction, hypertensive cardiac hypertrophy, and various cardiomyopathies.⁵ Considerable research interest has focused on the complex processes controlling cardiac myocyte mitochondrial biogenesis, including the key role of transcription factors such as peroxisomal proliferator activated receptors (PPAR) α and β, oestrogen-related receptors and upstream regulators, and PPARγ co-activator (PGC-1α).⁴ In this issue of Cardiovascular Research, Ventura-Clapier et al.⁶ review the role of PGC-1α in the regulation of mitochondrial biogenesis. Under normal conditions and in disease states, the authors discuss how down-regulation of PGC-1α expression is linked to mitochondrial dysfunction in heart failure. These studies are complemented by the review of Samuels et al.⁷ who address the genomic changes in mitochondrial function that occur in heart failure as well as other forms of heart disease. Samuels et al. address the molecular genetics, transcriptomics, and metabolomics of cardiac metabolism, providing key translational insights into the potential interaction between genomic variation and complex alterations in mitochondrial and cardiac metabolism relevant to cardiac pathological conditions.

While transcriptional control of mitochondrial function can occur in many pathological conditions, the review of Bray and Young⁸ demonstrates that many changes in metabolic gene expression occur in a diurnal manner. These authors review the exciting new advances in the area of cardiac function and circadian rhythm, including physiological and pathophysiological implications of diurnal alterations in cardiac metabolism. The impact of external signals on circadian rhythm on maladaptive changes in cardiac metabolism is also discussed.
3. Control of glycolysis

While glycolysis only provides 5–10% of the overall ATP requirements for the normal heart under normal conditions, it has been proposed that glycolysis serves to control membrane ion flux. During myocardial ischaemia, heart failure, and cardiac hypertrophy, the contribution of glycolysis to ATP production increases. The control of glycolysis is complex, and, like mitochondrial oxidative metabolism, relies on alterations in hormonal control, allosteric control, phosphorylation control, and transcriptional control. An important first step in the uptake of glucose is the transport of insulin through glucose transporters, primarily GLUT1 and GLUT4, the latter being highly responsive to insulin. The molecular signalling pathways that control insulin-stimulated glucose uptake have been the focus of considerable amount of research in the last decade. The paper of Bertrand et al. nicely reviews these molecular processes, including the critical role of the phosphatidylinositol 3-kinase (PI-3K) system and the Akt/PKB pathway. The paper also addresses derangements in myocardial insulin signalling relevant to diabetes and insulin resistance. Potential therapeutic options to improve insulin signalling are also addressed.

4. Signalling control of cardiac fatty acid metabolism

Fatty acids are normally the primary source of carbon substrate for the heart and originate either from free fatty acids bound to albumin in the blood or from triacylglycerol present in lipoproteins. The rates of fatty acid metabolism are controlled by the supply of fatty acids, the degree of expression of key metabolic proteins (enzymes and transporters), and the complex regulatory pathways including both allosteric regulation of enzymes and substrate–product relationships. In this issue of Cardiovascular Research, Schwenk et al. describe the key role of CD36 in controlling myocyte fatty acid uptake. This review also addresses the interplay between insulin and AMP-activated protein kinase (AMPK) in controlling these pathways. The authors raise the intriguing possibility that in addition to its key role in regulating glucose uptake, insulin may also serve a key role in regulating fatty acid uptake via CD36 translocation. They also discuss the role of alterations in CD36 translocation in mediating diabetes-induced changes in fatty acid uptake.

Once transported across the sarcolemma, fatty acids are subsequently activated by esterification to fatty acyl-CoA by fatty acyl-CoA synthetase. Acyl CoA moieties can either be esterified to intracellular lipids or converted to long-chain fatty acylcarnitine by carnitine palmitoyltransferase I (CPT-I). An important regulator of myocyte fatty acid uptake and oxidation is malonyl-CoA, a potent endogenous inhibitor of CPT-I. Thus, malonyl-CoA decreases the uptake of fatty acids into the mitochondria, thereby reducing mitochondrial fatty acid β-oxidation. The importance of malonyl-CoA control in regulating fatty acid oxidation rates as well as the control of malonyl-CoA by a troika of enzymes—AMPK, acetyl-CoA carboxylase, and malonyl-CoA decarboxylase—is discussed in the review by Ussher and Lopaschuk. The possibility of targeting these enzymes to treat various cardiac pathologies is also discussed.

Once fatty acids are taken up into the mitochondria, they subsequently undergo oxidation by a number of β-oxidative enzymes. The activity of the β-oxidative enzymes is highly regulated by both allosteric control and gene transcriptional control of their expression. Indeed, many of the enzymes of fatty acid β-oxidation are controlled by PGC-1α, PPARα, and PPARγ. Genomic analyses in various cardiac pathologies have demonstrated the importance of transcriptional control in determining the levels of these fatty acid oxidative enzymes. The original paper of Rennison et al. shows how the activity of the enzymes catalyzing the initial step of fatty acid β-oxidation, the acyl-CoA dehydrogenases, is decreased in heart failure. They also show, however, that the activity of acyl-CoA dehydrogenase can be increased with high-fat feeding, resulting in an improved mitochondrial function. At present, the importance of depressed mitochondrial fatty acid β-oxidation in heart failure as well as whether therapeutic approaches to treat heart failure should increase or decrease fatty acid oxidation are topics of substantial research interest.

5. Exogenous hormonal and substrate control of cardiac energy metabolism

Considerable recent interest has focused on how exogenous energy substrate supply to the heart can contribute to cardiac pathology. Exposure of the heart to high levels of fatty acids can result in the accumulation of fatty acid intermediates within the heart that can have deleterious effects on the heart. The mechanisms responsible for this ‘lipotoxicity’ are not completely understood, but are addressed in the review by Chess and Stanley. These authors also address the issue of ‘glucotoxicity’, where exposure of the heart to excess levels of glucose can lead to deleterious products of glucose metabolism. The role of diet in preventing heart failure from lipotoxicity and glucotoxicity is also addressed in this review. The original article by Bermudez et al. also examines how excess lipid supply to the heart in the form of triacylglycerol can contribute to vascular dysfunction by promoting lipid-mediated gene expression of genes involved in cell proliferation and inflammation. Hormones released from adipocytes (i.e. adipokines) have been shown to have significant actions on multiple organ systems, including the heart. This includes adipokines such as leptin and adiponectin. The role of adipokines on cardiac metabolic signalling pathways is discussed by Karmazyn et al. These authors also present a balanced view of how these adipokines can exert both salutary and deleterious effects on the heart. A better understanding of how these adipocyte signalling pathways function could identify some important therapeutic targets for treating heart diseases.

6. Conclusions

A plentiful and continuous production of energy is critical for the maintenance of cardiac function. The signalling pathways that ensure an adequate supply of energy to the heart are complex. We now know that the control of myocardial fuel metabolism becomes deranged in the diseased heart. Accordingly, it is important to understand how these pathways function. We hope that the articles in this
Spotlight issue will provide improved understanding of metabolic signalling pathways while providing a stimulus for further research in this area. A better understanding of these pathways should result in new therapeutic targets and strategies aimed at optimizing energy metabolism in order to prevent or treat heart failure.

References


