

Evolving Concepts of Myocardial Energy Metabolism

More Than Just Fats and Carbohydrates

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Although mitochondrial fatty acid and carbohydrate oxidation are the major source of ATP production in the heart, it is becoming increasingly clear that oxidation of other energy substrates, such as ketones and branched chain amino acids (BCAAs), can also contribute to energy production. Of importance is that alterations in cardiac ketone and branched chain amino acids metabolism may also impact the severity of heart failure through alterations in cellular signaling, despite these fuels providing a lower contribution to overall energy production.

Dating back to the first studies investigating glucose uptake in the isolated rabbit heart by Locke and Rosenheim in 1907 to the first studies in humans in the late 1940s by Richard Bing and colleagues assessing cardiac substrate extraction via measurement of arterial coronary sinus differences, cardiac energy metabolism has been a topic of interest for cardiologists and scientists alike. The importance of energy metabolism in the heart has become widely appreciated, as has the dynamic nature of the heart's ability to metabolize a wide range of energy substrates to meet its energy requirements. Fatty acids are recognized as a key source of energy for the heart, as well as carbohydrates, such as glucose and lactate (Figure).¹ In 1961, Shipp et al.² were the first to demonstrate that increasing fatty acid availability to the heart results in a marked inhibition of glucose oxidation, though credit for the reciprocal relationship between fatty acids and glucose metabolism (glucose/fatty acid cycle) is attributed to the work of Randle et al.³ Confirmation of Randle's glucose/fatty acid cycle in the rodent heart has since been demonstrated in the human heart.¹

Because the heart is the most metabolically demanding organ in the body, alterations in cardiac intermediary energy metabolism are major contributors to several cardiovascular pathologies. Some of these metabolic alterations include an increased reliance on fatty acids for oxidative energy production in the obese or diabetic heart, or a reduction in fatty

acid oxidation and increase in glycolysis in the decompensated failing heart.¹ To date, the vast majority of studies investigating intermediary energy metabolism in the normal and diseased myocardium have focused on carbohydrate and fatty acid metabolism, where oxidation of carbohydrates and fatty acids accounts for $\approx 90\%$ to 95% of ATP production in the heart. However, in light of recent findings demonstrating that metabolism of other substrates, such as BCAAs and ketone bodies, may be altered in various cardiovascular pathologies, the field has become increasingly aware that myocardial intermediary metabolism extends beyond fatty acids and carbohydrates. There have been several advances in our understanding of myocardial BCAA and ketone body metabolism, as well as their impact on cardiovascular disease pathology.

Energy Substrate Competition for Mitochondrial Oxidative Metabolism

It is widely accepted that glucose and fatty acids compete as a source of acetyl CoA for the tricarboxylic acid cycle and subsequent mitochondrial oxidative energy production (Figure). Based on this premise, it could be anticipated that in situations where circulating BCAAs or ketone bodies are elevated, such as diabetes mellitus or heart failure, that increased BCAA or ketone body oxidation would compete for tricarboxylic acid cycle acetyl CoA, resulting in an impairment of fatty acid or carbohydrate oxidation. However, what is often not considered is the actual percent contribution these fuels provide toward total myocardial oxidative ATP production. Indeed, few studies, to date, have measured actual flux for oxidation of BCAAs and other amino acids, with one study demonstrating a minimal contribution of leucine oxidation to overall energy production in the isolated rat heart (3%–5% of overall cardiac oxygen consumption rates).⁴ Likewise, few studies have determined actual flux rates in the heart for ketone body oxidation. Data in our laboratories support these limited findings because the presence of BCAAs or β -hydroxybutyrate (β HB) at clinically relevant concentrations has no effect on myocardial glucose and fatty acid oxidation rates in the isolated working mouse heart, with each substrate accounting for 10% at most of total ATP production (Figure; unpublished data). If ketone bodies and BCAAs are not major contributors to overall myocardial ATP production with negligible actions on myocardial carbohydrate and fatty acid oxidation, this leads to the important question of how altering energy metabolism of these substrate fuels impacts myocardial function during disease progression. Recent evidence illustrates that changes in myocardial ketone body and BCAA metabolism/oxidation modulate ventricular function via influencing various cardiac myocyte signaling processes (see below).

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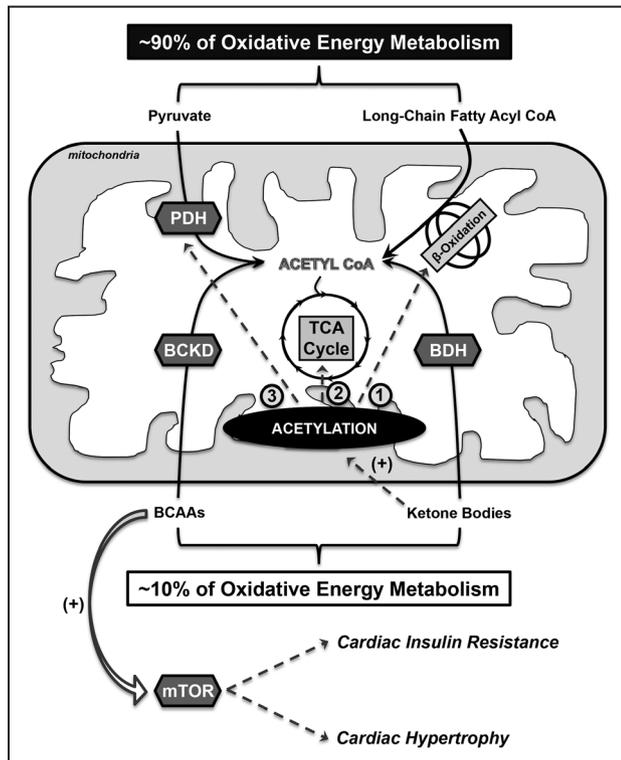


Figure. Interaction of energy substrates for oxidative energy production and branched chain amino acid (BCAA)/ketone body regulation of cellular signaling in the heart. The figure depicts how energy substrates compete for mitochondrial oxidative energy metabolism via generation of acetyl CoA for the tricarboxylic acid (TCA) cycle. However, as both BCAAs and ketone bodies are not major providers of overall acetyl CoA for oxidative energy metabolism, they may influence cardiac function and cardiovascular disease progression via regulating various cardiac signaling processes. This includes influencing mitochondrial protein acetylation or mTOR (mammalian target of rapamycin) signaling, both of which may influence important cardiac processes, such as insulin sensitivity and cellular growth. BCKD indicates branched chain α -keto acid dehydrogenase; BDH, β -hydroxybutyrate dehydrogenase; mTOR, mammalian target of rapamycin; and PDH, pyruvate dehydrogenase.

Energy Substrates as Signaling Molecules

In addition to being important energy substrates for the heart, fatty acids and their intermediates are also important signaling molecules. This includes acting as ligands for transcription factors, such as PPAR α (peroxisome proliferator-activated receptor α), serving as precursors for fatty acid derivatives, such as diacylglycerol and ceramides, while also impacting insulin signaling and modifying apoptosis.⁵ Hence, alterations in flux through fatty acid oxidation may potentially modify the levels of these fatty acid intermediates, thereby impacting these various signaling pathways. Glucose and glycolytic intermediates also have multiple signaling functions, and similar to fatty acids, altering glucose metabolism can impact these signaling pathways.

It is now clear that ketone bodies and BCAAs also have important roles in myocardial signaling. For instance, β HB can act at a nuclear level as an inhibitor of histone deacetylases, which can inhibit prohypertrophic transcription.⁶ Circulating β HB levels are decreased in obese females,⁷ as well as in obese

mice with heart failure,⁸ which can potentially contribute to the decrease in cardiac β HB and increased histone deacetylase activity, thereby increasing histone acetylation, leading to a decrease in forkhead box protein O1 acetylation and atrogen-1 expression, while also activating calcineurin/NFAT (nuclear factor of activated T-cells) signaling.⁶

BCAAs, such as leucine, can stimulate mTOR (mammalian target of rapamycin), which as part of the mTORC1 (mammalian target of rapamycin complex 1) complex has multiple functions in regulating cell growth/proliferation and insulin signaling through activating p70S6 kinase and increasing serine phosphorylation of the insulin-receptor substrate to block insulin signaling.⁹ In addition, accumulation of branched chain α -keto acids, the products of BCAAs, due to defects in BCAA oxidation, has also been proposed to promote insulin resistance.¹⁰

These energy substrates may also influence cardiac signaling via posttranslational modification of lysine acetylation, which has an important role in regulating mitochondrial metabolic pathways. Ketone body oxidation has recently been proposed to be an important source of acetyl CoA for this acetylation, and in the failing heart (both humans and animals), ketone body oxidation rates appear to be increased.^{8,11} This increase in ketone body oxidation may provide surplus acetyl CoA for mitochondrial protein hyperacetylation, which could possibly lead to metabolic rearrangements in the failing heart.

BCAA metabolism also seems to be affected by heart failure because a defect in BCAA metabolism into their corresponding branched chain α -keto acids (α -ketoisovalerate, α -ketoisocaproate, and α -keto- β -methylvalerate) is observed in the myocardium of both mice and humans with heart failure.¹⁰ Intriguingly, pharmacological interventions aimed at enhancing branched chain α -keto acid metabolism via inhibiting the kinase that phosphorylates and inhibits branched chain α -keto acid dehydrogenase improved ventricular function after pressure overload-induced heart failure.¹⁰

Of interest, advances in the field of small metabolites and cellular signaling have also revealed that various energy substrates and their metabolites bind receptors that are likely to influence several cellular signaling processes (eg, second messenger-mediated signal transduction). This includes the G-protein-coupled receptor GPR81, which lactate has been shown to activate in adipocytes,¹² or the G-protein-coupled receptor GPR109A, which is activated by β HB.⁶ Whether BCAAs also activate receptor-mediated mechanisms to influence cellular signaling remains to be determined, as is whether these receptors are even expressed in cardiac myocytes. These important questions will hopefully be answered by the field in coming years, and it will be important to determine whether these substrate fuels contribute to cardiac signaling or cardiovascular disease progression independently from their role in myocardial energy provision, which now seems to be a more realistic possibility.

Fuel Use and Cardiac Efficiency

It has long been recognized that there are significant disparities in the efficiency of different energy substrates in producing ATP.¹ In particular, although fatty acids are a plentiful

source of energy for the heart, they are less efficient than carbohydrates at producing ATP (ie, ATP produced per oxygen consumed).¹ How other energy substrates impact on cardiac efficiency is less well defined. Interest in this has come to the forefront with the recent demonstration that the SGLT2 inhibitor, empagliflozin, has profound cardioprotective effects in high-risk patients with diabetes mellitus.¹³ Because SGLT2 inhibitors also increase β HB levels, it has been suggested that this increases ketone body oxidation in the heart and that ketone bodies are a superfuel that is oxidized by the heart in preference to fatty acids and glucose, and that ketones not only improve cardiac function in the failing heart, but also improve cardiac efficiency.¹⁴ However, despite oxidation of β HB providing more energy per 2 carbon moiety than glucose or pyruvate, it actually produces less energy than oxidation of a fatty acid. Conversely, on the basis of ATP produced per oxygen consumed (P/O ratio), metabolism of β HB is more efficient than that of fatty acids, but less efficient than that of glucose. Because fatty acids, glucose, and β HB may all compete for tricarboxylic acid cycle acetyl CoA (Figure), increasing the metabolism of β HB should decrease glucose oxidation, thereby potentially actually decreasing cardiac efficiency. However, to date, the relationship between ketone body, fatty acid, and glucose oxidation and cardiac efficiency is not clear.

As mentioned previously, ketone body oxidation is increased in the failing heart. Whether this is an adaptive or maladaptive process is unclear. Although increased ketone body oxidation may maintain fuel supply for oxidative metabolism, the potential also exists for an increase in mitochondrial protein acetylation (which compromises cardiac energetics). Ketone body oxidation may also lead to a depletion of tricarboxylic acid cycle intermediates (ie, decreased anaplerosis), leading to a decrease in mitochondrial oxidative phosphorylation.¹⁵ Therefore, enhancing β HB oxidation in the setting of diabetes mellitus and heart failure may be potentially undesirable. Hence, the relationship between myocardial ketone body oxidation and cardiac efficiency remains enigmatic.

Implications for the Field of Myocardial Energy Metabolism

For decades, the field appreciated the importance of fatty acids and carbohydrates to myocardial energy metabolism and subsequent cardiac function and contractile efficiency. In the past decade, however, the field has become more aware that intermediary metabolism of other substrate fuels, such as BCAAs and ketone bodies, are also important contributors to cardiac function, especially in the context of underlying cardiac disease. It should be noted, though, that a lot of the landmark studies illustrating an important role for these fuels with regards to myocardial energy metabolism in health and disease were identified via unbiased metabolite profiling using metabolomics-based screening methods.^{8,10,11} Such findings highlight the power of unbiased metabolomics approaches to identify novel metabolic processes that may be implicated in disease pathogenesis, thereby acting as a hypothesis-generating tool that can lead to intricate molecular explorations in animal models of cardiovascular disease. On the contrary, these findings tell us nothing about the actual contribution to

myocardial ATP production because metabolomics assessments provide no information on actual substrate flux, and as already mentioned, work in our laboratories suggest that BCAAs and ketone bodies are not major providers of overall ATP production in the heart (unpublished data). Nonetheless, myocardial metabolism of BCAAs and ketone bodies is still important because they can influence several cellular signaling processes, some of which are key regulators of cellular growth that may influence the progression of cardiac hypertrophy.

Taken together, it is obvious that metabolism of various substrate fuels in the heart can influence cardiac function during the progression of several cardiovascular pathologies. However, it is now clear that the role(s) metabolism of these fuels play extends beyond energy provision to the myocardium, despite the primary role of intermediary metabolism in the heart being to support the massive energy demand for constant contractile activity. Future studies will have to take into account the numerous signaling processes influenced by the plethora of substrate fuels the heart simultaneously oxidizes. As such, understanding these cardiac signaling changes will likely yield a better understanding of whether targeting myocardial metabolism will be a feasible approach to treat cardiovascular disease, in comparison to a body of historical research that surmised either increasing cardiac energy production or enhancing contractile efficiency as the mechanisms of benefit.

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Disclosures

None.

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