Cardiovascular Drugs and Therapy
https://doi.org/10.1007/s10557-022-07320-4

BSCR MEMBER SUBMISSIONS

Branched-Chain Amino Acid Metabolism in the Failing Heart

Qutuba G. Karwi[1,2] · Gary D. Lopaschuk[1]

Accepted: 27 January 2022

Abstract
Branched-chain amino acids (BCAAs) are essential amino acids which have critical roles in protein synthesis and energy metabolism in the body. In the heart, there is a strong correlation between impaired BCAA oxidation and contractile dysfunction in heart failure. Plasma and myocardial levels of BCAA and their metabolites, namely branched-chain keto acids (BCKAs), are also linked to cardiac insulin resistance and worsening adverse remodelling in the failing heart. This review discusses the regulation of BCAA metabolism in the heart and the impact of depressed cardiac BCAA oxidation on cardiac energy metabolism, function, and structure in heart failure. While impaired BCAA oxidation in the failing heart causes the accumulation of BCAA and BCKA in the myocardium, recent evidence suggested that the BCAAs and BCKAs have divergent effects on the insulin signalling pathway and the mammalian target of the rapamycin (mTOR) signalling pathway. Dietary and pharmacological interventions that enhance cardiac BCAA oxidation and limit the accumulation of cardiac BCAAs and BCKAs have been shown to have cardioprotective effects in the setting of ischemic heart disease and heart failure. Thus, targeting cardiac BCAA oxidation may be a promising therapeutic approach for heart failure.

Keywords Branched-chain amino acids · Branched-chain keto acids · Heart failure · Cardiac insulin resistance · Glucose oxidation

Introduction

The heart has the highest energy demand of any organ in the human body [1]. Maintaining fuel supply and energy production to the heart is vital in sustaining its contractile function and ensuring body survival. However, the heart also has minimal energy storage capacity (in the form of adenosine triphosphate (ATP)). If not replenished, the heart will run out of ATP in just 2–10 s [1, 2], which leads to contractile failure. The heart also has limited ability for gluconeogenesis, lipogenesis, or ketogenesis. Therefore, the heart is equipped with complex and efficient machinery to utilize a variety of oxidative substrates to generate ATP. The ability of the heart to switch between different oxidative substrates gives the heart "metabolic flexibility" to adapt to different workloads, substrates availability and neurohormonal activity. The majority of cardiac ATP (~90%) is produced via mitochondrial oxidative metabolism, while glycolysis contributes ~10% of the heart's ATP production [3, 4]. Therefore, disrupted oxygen supply could compromise cardiac ATP production and lead to cardiac failure.

Fatty Acid, Glucose, Ketone, and BCAA Metabolism in the Normal Healthy Heart

Fatty acids are a major fuel source for the heart, and the mitochondrial ß-oxidation of fatty acid typically provides 40–60% of the heart's energy needs [5, 6]. Fatty acids are initially esterified, forming fatty acyl-CoA following uptake into the cardiomyocyte. The fatty acid moiety is then transferred to carnitine by carnitine palmitoyltransferase 1 (CPT-1) in the cytosol to form a long-chain acylcarnitine [7], which is then shuttled to the mitochondria. The fatty acid group is again transferred to CoA to form fatty acyl-CoA, which enters β-oxidation to produce acetyl-CoA, which feeds into the tricarboxylic acid (TCA) cycle [1, 8]. Glucose is another primary substrate in the heart, and it contributes 20–40% of the heart's energy needs [9]. Glucose is mainly

✉ Gary D. Lopaschuk
gary.lopaschuk@ualberta.ca

[1] Cardiovascular Research Centre, University of Alberta, Edmonton, AB T6G 2S2, Canada

[2] Department of Pharmacology, College of Medicine, University of Diyala, Diyala, Iraq

Published online: 12 February 2022

taken up into the cardiomyocyte via insulin-independent and insulin-dependent glucose transporters (GLUT), namely GLUT1 and GLUT4, respectively. Although the heart is an insulin-sensitive organ and insulin markedly stimulates cardiac glucose uptake, the contribution of insulin-dependent vs insulin-independent glucose uptake in the heart is still not clear and needs to be directly investigated. Glucose is converted to pyruvate and generates ATP via glycolysis (2 ATP/glucose molecule) in the cytosol [1, 2]. Pyruvate is taken up by the mitochondria via the mitochondrial pyruvate carrier (MPC) and oxidized via mitochondrial glucose oxidation (29 ATP/2 molecules of pyruvate) [1, 2].

Ketone bodies, namely β-hydroxybutyrate (βOHB), acetoacetate (AcAc), and acetone, also contribute around 15–20% of the overall cardiac ATP production [10, 11]. Ketone bodies are taken up by the heart via SLC16A1 and transported to the mitochondria, where βOHB, the major ketone body in the heart, is oxidized to AcAc via β-hydroxybutyrate dehydrogenase 1 (BDH1) [11]. AcAc is then converted to acetoacetyl-CoA (AcAc CoA) by succinyl-CoA:3 oxoacid-CoA transferase (SCOT), which is then converted to acetyl CoA via thiolase. The heart can readily oxidize ketone bodies, and ketone bodies' contribution as a source of acetyl CoA for the TCA cycle increases when circulating ketone body levels increase [10].

The heart can also utilize a variety of amino acids, including branched-chain amino acids (BCAAs), glutamate, cystine, histidine, and lysine, as a source of fuel. Among the nine essential amino acids, leucine, isoleucine, and valine have a branched aliphatic side chain and thus are grouped as BCAAs. Meat, fish, egg, and dairy products have a high content of BCAAs. Similar to other amino acids, BCAAs play an important role in protein synthesis and neurotransmitter synthesis [12–16]. In addition, BCAAs also modulate food intake and glycemic control via influencing hormones release, such as leptin, glucagon-like peptide-1, and ghrelin [17–19] (see [20, 21] for a general review of BCAA metabolism). In the heart mitochondria, BCAAs undergo transamination. They are converted to their correspondent branched-chain keto acids (BCKAs), namely α-ketoisocaproate (produced from leucine), α-keto-β-methylvalerate (produced from isoleucine), and α-ketovalerate (produced from valine), by mitochondrial branched-chain amino-transaminase (BCATm) (Fig. 1) [1, 2, 21]. Transamination by BCATm is a reversible process, which can convert BCKAs back to BCAAs [22]. BCKA is then acted on by mitochondrial branched-chain α-keto acid dehydrogenase (BCKDH) and is eventually converted to either acetyl-CoA for the TCA cycle or succinyl-CoA for anaplerosis [1, 21]. BCKDH activity is dependent on its phosphorylation status, where it is dephosphorylated and activated by mitochondrial protein phosphatase 2C (PPC2m) [23] or phosphorylated and inhibited by mitochondrial branched-chain α-keto acid dehydrogenase kinase (BCKDK) [24]. Direct measurement of BCAA oxidation in vivo shows that they are only a minor fuel source for the heart, contributing to ~ 1–2% of the overall cardiac ATP production [6, 25].

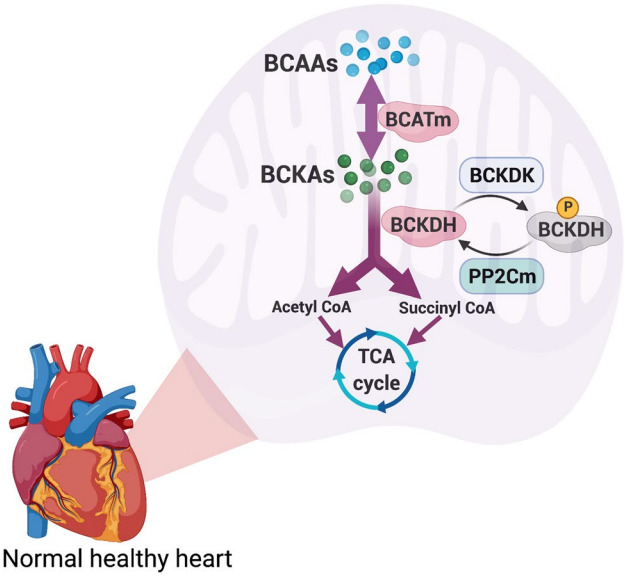

Fig. 1 Branched-chain amino acid (BCAA) metabolism in the normal heart. BCAAs are taken up by the cardiomyocyte and transported to the mitochondria, where the BCAAs are converted to branched-chain keto acids (BCKAs) by mitochondrial branched-chain aminotransferase (BCATm). BCKAs are then used by branched-chain acid α-keto acid dehydrogenase (BCKDH) to eventually produce acetyl CoA and succinyl CoA that feeds into the tricarboxylic acid (TCA) cycle. BCKDH is phosphorylated and inactivated by phosphorylation of branched-chain α-keto acid dehydrogenase kinase (BCKDK), while it is dephosphorylated and activated by mitochondrial protein phosphatase 2 C (PP2Cm)

BCAA Metabolism in the Failing Heart

Compromised cardiac energy metabolism is a major contributor to the development of heart failure and a key determinant of its progression [1, 26]. While heart failure is multifactorial, there is a consensus that the failing heart is an "engine out of fuel" [26] due to altered heart preference for oxidative substrates and disrupted mitochondrial oxidative phosphorylation. Alterations in cardiac preference for oxidative substrates and how these alterations influence heart failure severity were comprehensively reviewed elsewhere (see [1] for review). Here, we review the current knowledge of the changes in BCAA metabolism that occur in heart failure and how these changes impact cardiac function, structure, and energy metabolism. Despite their minor role as fuel to support contractile function in the heart, BCAAs are important signalling molecules that can influence cardiac energy metabolism via modulating signalling pathways in

the heart, such as the insulin signalling pathway and the mammalian target of rapamycin (mTOR) signalling pathway. Elevated levels of circulating BCAAs and BCKAs have been proposed to be a predictor of coronary heart disease (Fig. 2) [27–29], congestive heart failure [30], and the incidence of cardiovascular disease [31–33] in human. Similarly, augmented levels of circulating BCAAs and BCKAs are also seen in preclinical models of myocardial infarction [34, 35], myocardial ischemia/reperfusion injury [36], and heart failure [37, 38]. We propose that the high levels of BCAAs and BCKAs seen in heart failure can negatively impact cardiac function by acting as signalling molecules to negatively impact cardiac energy metabolism.

High plasma levels of BCAA and BCKA have the potential to increase BCAA contribution to the cardiac ATP production in the failing heart. However, it is unlikely that this could improve energy production in the failing heart due to the minimal contribution of BCAA to cardiac ATP production. For example, BCAA contributes to ~ 2% of the total cardiac ATP production [6, 25], so doubling this contribution, mainly driven by elevated plasma BCAA levels, would only account o ~ 4% of total cardiac ATP production. Regardless, emerging data suggests that BCAA oxidation is impaired in the failing heart, contributing to the rise in BCAA and BCKA levels in the failing heart. Studies have shown that BCAA oxidation key enzymes expressions are downregulated in experimental models of compensated heart failure [39], decompensated heart failure [39], and dilated cardiomyopathy [38]. BCAA oxidation enzyme protein levels are also decreased in a mouse model of dilated cardiomyopathy [40], accompanied by accumulation of BCAAs [40] and BCKAs [38] in failing hearts. In line with that, ex vivo preclinical studies have shown that BCAA oxidation is impaired in murine models of ischemia/reperfusion injury [36], myocardial infarction [34, 41], and pressure-overload-induced heart failure [41]. The accumulation of BCAAs and BCKAs in heart failure has been linked to activating the mTOR signalling pathway, a critical hypertrophic signalling pathway, in murine models of heart failure (Fig. 2) [34, 42]. For instance, whole-body BCATm deletion impairs BCAA oxidation and significantly increases circulating BCAA levels and accumulation of cardiac BCAAs [43]. Accumulation of cardiac BCAAs is accompanied by triggering the mTOR signalling pathway and hypertrophy of the heart, kidneys, and spleen [43]. Significantly, cardiac hypertrophy can be reversed by feeding BCATm knockout mice a diet

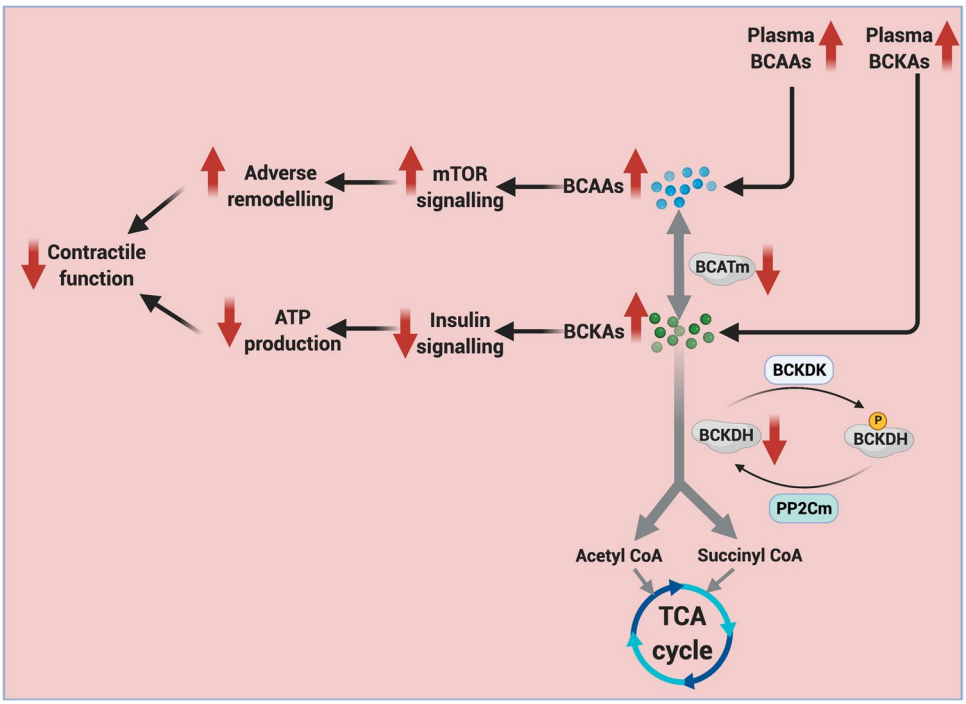

Fig. 2 Alteration in plasma levels and oxidation of cardiac branched-chain amino acids (BCAAs) in heart failure. Circulating BCAA and BCKA levels are elevated in heart failure. Cardiac BCAA oxidation rates are impaired in the failing heart, associated with the accumulation of BCAA and BCKA in the myocardium. Accumulation of BCAA is more important than BCKAs in triggering the mammalian target of rapamycin (mTOR) signalling pathway and worsening adverse remodelling in the failing heart. In contrast, BCKA accumulation inhibits the cardiac insulin signalling pathway and insulin-stimulated cardiac glucose oxidation, which negatively impacts cardiac adenosine triphosphate (ATP) production. Collectively, impaired cardiac BCAA oxidation rates further aggravate contractile dysfunction in the failing heart. *BCATm* mitochondrial branched-chain aminotransferase, *BCKDH* branched-chain acid alpha-keto acid dehydrogenase, *BCKDK* branched-chain acid alpha-keto acid dehydrogenase kinase, *PP2Cm* mitochondrial protein phosphatase 2 C

supplemented with rapamycin, suggesting that mTOR is the primary mediator of BCAAs-induced cardiac hypertrophy [43]. Recently, we have shown that cardiac-specific deletion of BCATm causes a significant increase in cardiac BCAA levels along with a significant reduction in cardiac BCKA levels and BCAA oxidation rates ex vivo, with no significant effect on circulating BCAA or BCKA levels [44]. This BCAA accumulation in the BCATm deficient heart triggers the mTOR signalling pathway and causes cardiac hypertrophy [44]. In further support of that, studies have also demonstrated that enhancing BCAA oxidation or inhibition of mTOR can improve cardiac function [38]. Furthermore, BCAAs supplementation following myocardial infarction aggravates cardiac hypertrophy and further deteriorates cardiac function in the infarcted mouse heart [35].

One of the significant metabolic alterations that occur in the failing heart is cardiac insulin resistance, mainly due to impaired cardiac insulin signalling in preclinical models and human [45–57]. Insulin plays a critical metabolic role in the heart, regulating cardiac reliance on fatty acid and glucose for energy production. Cardiac insulin resistance is mainly manifested by a decrease in insulin-stimulated glucose uptake and insulin-stimulated glucose oxidation, changes that negatively impact cardiac energy metabolism in heart failure [45–57]. Moreover, cardiac insulin resistance further aggravates contractile dysfunction in heart failure [45–55]. In addition, cardiac insulin resistance seen in obesity or heart failure is exacerbated if both co-exist in preclinical models and humans [34, 58–64]. Of importance is that impaired cardiac BCAA oxidation enzymes expressions and activities have been linked to worsening of cardiac insulin resistance and cardiac dysfunction in heart failure patients and murine models of aortic constriction [38], myocardial infarction [34], and myocardial ischemia/reperfusion [36]. Furthermore, augmented BCAA [36] and BCKA [65] levels inhibit the activity of the pyruvate dehydrogenase (PDH) enzyme, the rate-limiting enzyme in mitochondrial glucose oxidation, that further limits glucose oxidation in the failing heart [34]. While the association between the alterations in BCAA metabolism and different types of heart diseases, including heart failure with reduced ejection fraction, myocardial infarction, and ischemia/reperfusion injury, compensated and decompensated heart failure has been reported, and it is still not clear whether this association also occur in other types of heart failure such as diabetic cardiomyopathy, heart failure with preserved ejectin fraction, or end-stage heart failure.

Since impaired BCAA oxidation leads to the accumulation of cardiac BCAAs and BCKAs, the question is raised whether the BCAAs or the BCKAs are more important in mediating cardiac insulin resistance and cardiac hypertrophy. Delineating how these metabolites influence insulin and mTOR signals are challenging because BCAAs can be converted to BCKAs and vice versa via the BCATm enzyme. Recent studies have shown that acute exposure of the heart to high levels of α-ketoisovalerate ex vivo increases valine levels [66]. However, it is not clear how the accumulation of valine in the myocardium influences insulin signalling, energy metabolism, cardiac function, or structure [66]. However, we recently generated a mouse colony where BCATm is specifically deleted from the heart ($BCATm^{Cardiac-/-}$), which offers the opportunity to delineate the role of BCAA from those of BCKA on cardiac hypertrophy and insulin signalling [44]. Cardiac-specific deletion of BCATm causes a significant increase in cardiac BCAA levels and a significant decrease in cardiac BCKA levels while also decreasing cardiac BCAA oxidation rates ex vivo [44]. Interestingly, BCAA accumulation in the $BCATm^{Cardiac-/-}$ hearts was accompanied by activation of the cardiac mTOR signalling pathway and increased left ventricular mass. Since BCAA levels are increased in these hearts, it suggests that BCAAs, not BCKAs, trigger the hypertrophic signalling in the heart [44].

Of interest, the decreased cardiac BCKA levels in the $BCATm^{Cardiac-/-}$ hearts are associated with enhanced cardiac insulin signalling and insulin-stimulated glucose oxidation rates ex vivo [44]. Since BCAA levels are decreased in these hearts, these findings suggest that BCKAs, not BCAAs, have an inhibitory effect on cardiac insulin signalling. In further support of this, perfusing normal and healthy mice hearts with high levels of BCKAs, in the absence of BCAAs, inhibits cardiac insulin signalling and abolishes insulin-stimulated glucose oxidation rates ex vivo [44]. Of importance is that high BCKA levels ex vivo have no significant effect on cardiac mTOR activity [44]. Together, these data support divergent effects of BCAAs and BCKAs on insulin signalling and mTOR signalling in the heart.

Therapeutic Strategies Targeting BCAA Metabolism to Treat Heart Failure

Recognizing the detrimental effects of augmented levels of plasma BCAA and BCKA and impaired cardiac BCAA oxidation on cardiac energy metabolism, function, and structure, different approaches have been explored to enhance cardiac BCAA oxidation and reduce plasma levels of BCAA in preclinical models of heart failure [35–38]. One of the potential targets to enhance BCAA oxidation and reduce the accumulation of cardiac BCAAs is via stimulating BCATm enzyme. Acute inhibition of BCAT in the whole body, using an orally active BCAT inhibitor (2-[(4-chloro-2,6-difluorobenzyl)amino]-7-oxo-5-propyl-4,7-dihydropyrazolo(1,5-a)-pyrimidine-3-carbonitrile), causes a significant increase in the plasma levels of BCAA [67], suggesting impaired whole-body BCAA oxidation.

Therefore, enhancing flux through BCATm can increase BCAA oxidation and reduce cardiac levels of BCAA, which could have beneficial effects in reducing adverse remodelling in the failing heart. We have recently provided the first direct evidence that selective increase in cardiac BCAA levels by cardiac-specific deletion of BCATm triggers cardiac hypertrophy via stimulating the mTOR signalling pathway [44]. In addition, cardiac-specific deletion of BCATm markedly decreases cardiac BCKA levels and enhances insulin-stimulated cardiac glucose oxidation rates ex vivo [44]. However, it should be emphasized that increasing the flux through BCATm can potentially increase cardiac BCKA levels (Fig. 3A). This is significant since we have demonstrated that BCKAs exert an inhibitory effect on cardiac insulin signalling and insulin-stimulated glucose oxidation rates ex vivo [44]. However, the challenge with inhibiting BCATm activity is that it will lead to the accumulation of BCAA (Fig. 3B), which can trigger the mTOR signalling and causes cardiac hypertrophy [44]. Therefore, targeting BCATm may not be a plausible therapeutic approach to treat heart failure, although this needs to be directly investigated.

Another approach to target BCAA oxidation is via stimulating BCKDH enzyme. Compared to BCATm, enhancing the flux through BCKDH enhances BCAA oxidation and decreases both BCAA and BCKA levels. For instance, 3,6-dichlorobenzo(b)thiophene-2-carboxylic acid (BT2) is an allosteric inhibitor of BCKDK enzyme [68], which (by inhibiting BCKDH phosphorylation) increases BCAA oxidation by enhancing the activity of BCKDH (Fig. 3C). Thus, treatment with BT2 enhances cardiac function and mitigates adverse remodelling in murine models of ischemic and failing hearts by promoting BCAA oxidation not only in the heart but in the whole body. It is worth mentioning that the contribution of accelerating whole-body BCAA metabolism in the cardioprotection established by BT2 treatment is still not clear. Nevertheless, studies have shown that BT2 treatment reduces the accumulation of cardiac BCAAs [40, 69] and BCKAs [38, 69].

BCAA oxidation could also be modulated by altering PP2Cm, the enzyme that dephosphorylates and activates BCKDH (Fig. 3D). Studies have shown that PP2Cm deletion impairs cardiac BCAA oxidation, as evidenced by increased BCAA and BCKA levels in the mouse heart [38]. Furthermore, PP2Cm deletion increases the heart's vulnerability to contractile dysfunction in a mouse model of pressure-overload-induced heart failure [38]. It has also been proposed that the accumulation of cardiac BCKA could negatively impact mitochondrial energetics. For example, incubation of heart mitochondria with high levels of BCKAs in vitro inhibits the activity of complex I, but not complex II, in a dose-dependent manner [38]. BCKAs accumulation in PP2Cm-deficient mitochondria in vitro promotes superoxide production and increases carbonylation levels in the mitochondria [38]. These findings suggest that BCKAs may

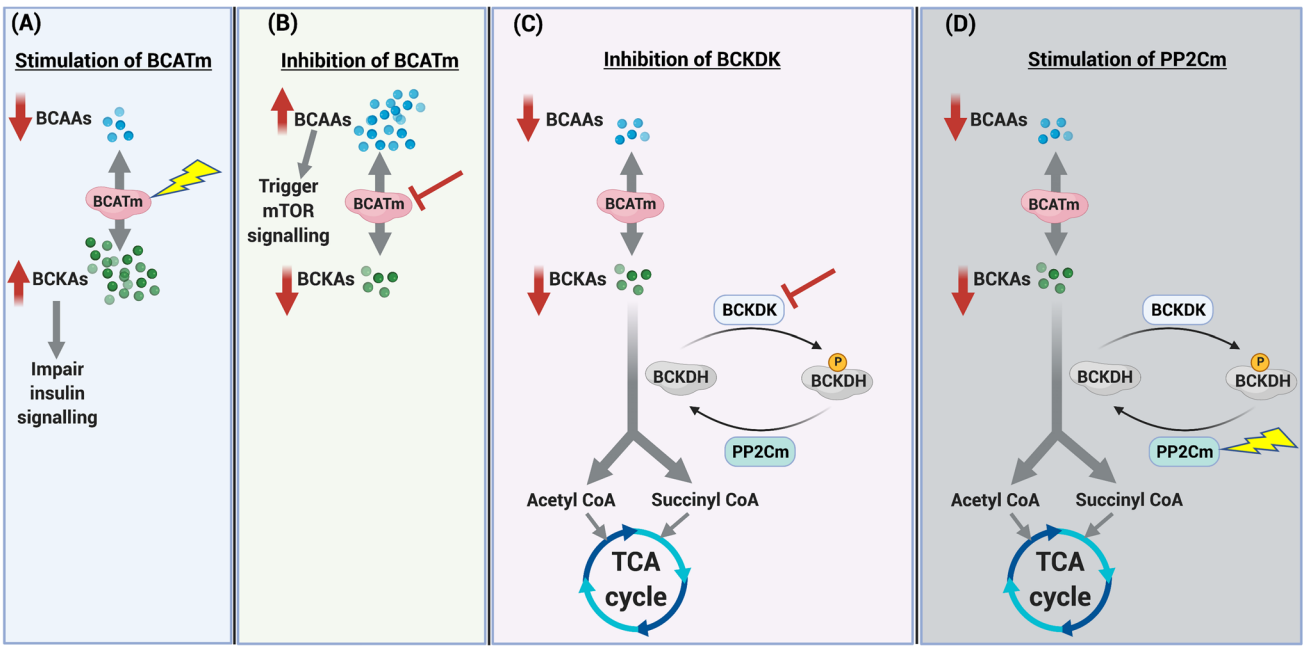

Fig. 3 Therapeutic targets manipulating BCAA metabolism and their impacts on cardiac BCAA and BCKA levels. **A** Stimulation of mitochondrial branched-chain aminotransferase (BCATm) decreases cardiac BCAA levels while increasing cardiac BCKA levels, which can impair cardiac insulin signalling. **B** Inhibition of BCATm decreases cardiac BCKAs levels while increasing cardiac BCAA levels, triggering the mammalian target of rapamycin (mTOR) signalling pathway. **C** Inhibition of branched-chain acid alpha-keto acid dehydrogenase kinase (BCKDK) or **D** stimulation of mitochondrial protein phosphatase 2 C (PP2Cm) decreases both cardiac BCAAs and BCKAs

directly influence mitochondrial bioenergetics and enhance oxidative injury to cardiac proteins. However, the exact mechanism(s) through which these effects are mediated are yet to be determined.

Dietary interventions to reduce BCAA and BCKA supply to the heart have also been explored. For example, restricting BCAAs in the diet of Zucker fatty rats showed a beneficial effect on cardiac ATP production and reduced triacylglycerol levels via promoting fatty acid utilization. However, the mechanism is not known yet [70]. Moreover, recent studies have shown that weight loss during lifestyle intervention enhances BCAA catabolism and improves insulin sensitivity in adolescence with obesity [71].

Conclusions

Alterations in cardiac BCAA oxidation are linked to cardiac insulin resistance and adverse remodelling in the failing heart. Cardiac BCAA oxidation is impaired in heart failure due to the downregulation of its key enzymes, resulting in the accumulation of both BCAAs and BCKAs in the failing heart. BCAAs and BCKAs seem to have more important roles as signalling molecules than oxidative substrates for the heart. Recently evidence suggests that BCAAs are more critical in triggering the mTOR signalling pathway and promoting cardiac hypertrophy in the failing heart. At the same time, BCKAs have an inhibitory effect on cardiac insulin signalling and insulin-stimulated glucose oxidation. Of importance, pharmacological targeting of BCAA oxidation has emerged as a novel therapeutic approach to improving cardiac function, reducing adverse remodelling, and mitigating cardiac insulin resistance in heart failure.

Author Contribution QGK and GDL conducted the literature search, critically appraised the literature, and wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding GDL is funded by a Canadian Institute for Health Research Foundation Grant and a Heart and Stroke Foundation of Canada Grants. QGK is supported by an Alberta Innovates Postgraduate Fellowship in Health Innovation.

Data Availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Research Involving Human Participants and/or Animals Not applicable.

Informed Consent Not applicable.

Ethics Approval and Consent to Participate This is a review article, and the University of Alberta Research Ethics Committee has confirmed that no ethical approval is required.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

References

1. Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac energy metabolism in heart failure. Circ Res. 2021;128:1487–513.
2. Karwi QG, Uddin GM, Ho KL, Lopaschuk GD. Loss of metabolic flexibility in the failing heart. Front Cardiovasc Med. 2018;5:68.
3. Saddik M, Lopaschuk GD. Myocardial triglyceride turnover and contribution to energy substrate utilization in isolated working rat hearts. J Biol Chem. 1991;266:8162–70.
4. Wisneski JA, Stanley WC, Neese RA, Gertz EW. Effects of acute hyperglycemia on myocardial glycolytic activity in humans. J Clin Invest. 1990;85:1648–56.
5. Fukushima A, Zhang L, Huqi A, Lam VH, Rawat S, Altamimi T, Wagg CS, Dhaliwal KK, Hornberger LK, Kantor PF, et al. Acetylation contributes to hypertrophy-caused maturational delay of cardiac energy metabolism. JCI Insight. 2018:3.
6. Murashige D, Jang C, Neinast M, Edwards JJ, Cowan A, Hyman MC, Rabinowitz JD, Frankel DS, Arany Z. Comprehensive quantification of fuel use by the failing and nonfailing human heart. Science. 2020;370:364–8.
7. Murthy MS, Pande SV. Malonyl-CoA binding site and the overt carnitine palmitoyltransferase activity reside on the opposite sides of the outer mitochondrial membrane. Proc Natl Acad Sci USA. 1987;84:378–82.
8. Karwi QG, Jorg AR, Lopaschuk GD. Allosteric, transcriptional and post-translational control of mitochondrial energy metabolism. Biochem J. 2019;476:1695–712.
9. Karwi QG, Wagg CS, Altamimi TR, Uddin GM, Ho KL, Darwesh AM, Seubert JM, Lopaschuk GD. Insulin directly stimulates mitochondrial glucose oxidation in the heart. Cardiovasc Diabetol. 2020;19:207.
10. Ho KL, Karwi QG, Wagg C, Zhang L, Vo K, Altamimi T, Uddin GM, Ussher JR, Lopaschuk GD. Ketones can become the major fuel source for the heart but do not increase cardiac efficiency. Cardiovasc Res. 2020.
11. Karwi QG, Biswas D, Pulinilkunnil T, Lopaschuk GD. Myocardial ketones metabolism in heart failure. J Card Fail. 2020;26:998–1005.
12. Brosnan JT, Brosnan ME. Branched-chain amino acids: enzyme and substrate regulation. J Nutr. 2006;136:207S-211S.
13. Nie C, He T, Zhang W, Zhang G, Ma X. Branched chain amino acids: beyond nutrition metabolism. Int J Mol Sci. 2018;19:954.
14. Harper A, Miller R, Block K. Branched-chain amino acid metabolism. Annu Rev Nutr. 1984;4:409–54.
15. Lu G, Sun H, She P, Youn J-Y, Warburton S, Ping P, Vondriska TM, Cai H, Lynch CJ, Wang Y. Protein phosphatase 2Cm is a critical regulator of branched-chain amino acid catabolism in mice and cultured cells. J Clin Investig. 2009;119:1678–87.
16. Chou PY, Fasman GD. Structural and functional role of leucine residues in proteins. J Mol Biol. 1973;74:263–81.
17. Torres-Leal FL, Fonseca-Alaniz MH, Teodoro GF, de Capitani MD, Vianna D, Pantaleão LC, Matos-Neto EM, Rogero MM, Donato J, Tirapegui J. Leucine supplementation improves adiponectin and total cholesterol concentrations despite the lack of

changes in adiposity or glucose homeostasis in rats previously exposed to a high-fat diet. Nutr Metab. 2011;8:62.
18. Potier M, Darcel N, Tomé D. Protein, amino acids and the control of food intake. Curr Opin Clin Nutr Metab Care. 2009;12:54–8.
19. Chen Q, Reimer RA. Dairy protein and leucine alter GLP-1 release and mRNA of genes involved in intestinal lipid metabolism in vitro. Nutrition. 2009;25:340–9.
20. White PJ, Newgard CB. Branched-chain amino acids in disease. Science. 2019;363:582–3.
21. Neinast M, Murashige D, Arany Z. Branched chain amino acids. Annu Rev Physiol. 2019;81:139–64.
22. Sweatt AJ, Wood M, Suryawan A, Wallin R, Willingham MC, Hutson SM. Branched-chain amino acid catabolism: unique segregation of pathway enzymes in organ systems and peripheral nerves. Am J Physiol Endocrinol Metab. 2004;286:E64–76.
23. Lu G, Sun H, She P, Youn JY, Warburton S, Ping P, Vondriska TM, Cai H, Lynch CJ, Wang Y. Protein phosphatase 2Cm is a critical regulator of branched-chain amino acid catabolism in mice and cultured cells. J Clin Invest. 2009;119:1678–87.
24. Suryawan A, Hawes JW, Harris RA, Shimomura Y, Jenkins AE, Hutson SM. A molecular model of human branched-chain amino acid metabolism. Am J Clin Nutr. 1998;68:72–81.
25. Fillmore N, Wagg CS, Zhang L, Fukushima A, Lopaschuk GD. Cardiac branched-chain amino acid oxidation is reduced during insulin resistance in the heart. Am J Physiol Endocrinol Metab. 2018;315:E1046-E1052.
26. Neubauer S. The failing heart — an engine out of fuel. N Engl J Med. 2007;356:1140–51.
27. Bhattacharya S, Granger CB, Craig D, Haynes C, Bain J, Stevens RD, Hauser ER, Newgard CB, Kraus WE, Newby LK, et al. Validation of the association between a branched chain amino acid metabolite profile and extremes of coronary artery disease in patients referred for cardiac catheterization. Atherosclerosis. 2014;232:191–6.
28. Shah SH, Bain JR, Muehlbauer MJ, Stevens RD, Crosslin DR, Haynes C, Dungan J, Newby LK, Hauser ER, Ginsburg GS, et al. Association of a peripheral blood metabolic profile with coronary artery disease and risk of subsequent cardiovascular events. Circ Cardiovasc Genet. 2010;3:207–14.
29. Shah SH, Sun JL, Stevens RD, Bain, JR, Muehlbauer MJ, Pieper KS, Haynes C, Hauser ER, Kraus WE, Granger CB, et al. Baseline metabolomic profiles predict cardiovascular events in patients at risk for coronary artery disease. Am Heart J. 2012;163:844–850 (e841).
30. Peterson MB, Mead RJ, Welty JD. Free amino acids in congestive heart failure. J Mol Cell Cardiol. 1973;5:139–47.
31. Ruiz-Canela M, Toledo E, Clish CB, Hruby A, Liang L, Salas-Salvadó J, Razquin C, Corella D, Estruch R, Ros E, et al. Plasma branched-chain amino acids and incident cardiovascular disease in the PREDIMED trial. Clin Chem. 2016;62:582–92.
32. Magnusson M, Lewis GD, Ericson U, Orho-Melander M, Hedblad B, Engstrom G, Ostling G, Clish C, Wang TJ, Gerszten RE, et al. A diabetes-predictive amino acid score and future cardiovascular disease. Eur Heart J. 2013;34:1982–9.
33. Venturini A, Ascione R, Lin H, Polesel E, Angelini GD, Suleiman MS. The importance of myocardial amino acids during ischemia and reperfusion in dilated left ventricle of patients with degenerative mitral valve disease. Mol Cell Biochem. 2009;330:63–70.
34. Karwi QG, Zhang L, Wagg CS, Wang W, Ghandi M, Thai D, Yan H, Ussher JR, Oudit GY, Lopaschuk GD. Targeting the glucagon receptor improves cardiac function and enhances insulin sensitivity following a myocardial infarction. Cardiovasc Diabetol. 2019;18:1.
35. Wang W, Zhang F, Xia Y, Zhao S, Yan W, Wang H, Lee Y, Li C, Zhang L, Lian K, et al. Defective branched chain amino acid catabolism contributes to cardiac dysfunction and remodeling following myocardial infarction. Am J Physiol Heart Circ Physiol. 2016;311:H1160–9.
36. Li T, Zhang Z, Kolwicz SC Jr, Abell L, Roe ND, Kim M, Zhou B, Cao Y, Ritterhoff J, Gu H, et al. Defective branched-chain amino acid catabolism disrupts glucose metabolism and sensitizes the heart to ischemia-reperfusion injury. Cell Metab. 2017;25:374–85.
37. Uddin GM, Zhang L, Shah S, Fukushima A, Wagg CS, Gopal K, Al Batran R, Pherwani S, Ho KL, Boisvenue J, et al. Impaired branched chain amino acid oxidation contributes to cardiac insulin resistance in heart failure. Cardiovasc Diabetol. 2019;18: 86.
38. Sun H, Olson KC, Gao C, Prosdocimo DA, Zhou M, Wang Z, Jeyaraj D, Youn JY, Ren S, Liu Y, et al. Catabolic defect of branched-chain amino acids promotes heart failure. Circulation. 2016;133:2038–49.
39. Lai L, Leone TC, Keller MP, Martin OJ, Broman AT, Nigro J, Kapoor K, Koves TR, Stevens R, Ilkayeva OR, et al. Energy metabolic reprogramming in the hypertrophied and early stage failing heart: a multisystems approach. Circ Heart Fail. 2014;7:1022–31.
40. Uddin GM, Zhang L, Shah S, Fukushima A, Wagg CS, Gopal K, Al Batran R, Pherwani S, Ho KL, Boisvenue J, et al. Impaired branched chain amino acid oxidation contributes to cardiac insulin resistance in heart failure. Cardiovasc Diabetol. 2019;18:019–0892.
41. Sansbury BE, DeMartino AM, Xie Z, Brooks AC, Brainard RE, Watson LJ, DeFilippis AP, Cummins TD, Harbeson MA, Brittian KR, et al. Metabolomic analysis of pressure-overloaded and infarcted mouse hearts. Circ Heart Fail. 2014;7:634–42.
42. Shao D, Villet O, Zhang Z, Choi SW, Yan J, Ritterhoff J, Gu H, Djukovic D, Christodoulou D, Kolwicz SC Jr, et al. Glucose promotes cell growth by suppressing branched-chain amino acid degradation. Nat Commun. 2018;9:2935.
43. Neishabouri SH, Hutson SM, Davoodi J. Chronic activation of mTOR complex 1 by branched chain amino acids and organ hypertrophy. Amino Acids. 2015;47:1167–82.
44. Uddin GM, Karwi QG, Pherwani S, Gopal K, Wagg CS, Biswas D, Atnasious M, Wu Y, Wu G, Zhang L, et al. Deletion of BCATm increases insulin-stimulated glucose oxidation in the heart. Metabolism. 2021;124: 154871.
45. Swan JW, Anker SD, Walton C, Godsland IF, Clark AL, Leyva F, Stevenson JC, Coats AJ. Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure. J Am Coll Cardiol. 1997;30:527–32.
46. Vardeny O, Gupta DK, Claggett B, Burke S, Shah A, Loehr L, Rasmussen-Torvik L, Selvin E, Chang PP, Aguilar D, et al. Insulin resistance and incident heart failure the ARIC study (Atherosclerosis Risk in Communities). JACC Heart Fail. 2013;1:531–6.
47. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321:405–12.
48. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol. 2009;53:1925–32.
49. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. JACC Heart Fail. 2013;1:93–102.
50. Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. Am J Med Sci. 2001;321:225–36.
51. Lauer MS, Anderson KM, Kannel WB, Levy D. The impact of obesity on left ventricular mass and geometry. The Framingham Heart Study. JAMA. 1991;266:231–6.
52. Riehle C, Abel ED. Insulin signaling and heart failure. Circ Res. 2016;118:1151–69.

53. Fu F, Zhao K, Li J, Xu J, Zhang Y, Liu C, Yang W, Gao C, Li J, Zhang H, et al. Direct evidence that myocardial insulin resistance following myocardial ischemia contributes to post-ischemic heart failure. Sci Rep. 2015;5:17927.
54. Ciccarelli M, Chuprun JK, Rengo G, Gao E, Wei Z, Peroutka RJ, Gold JI, Gumpert A, Chen M, Otis NJ, et al. G protein-coupled receptor kinase 2 activity impairs cardiac glucose uptake and promotes insulin resistance after myocardial ischemia. Circulation. 2011;123:1953–62.
55. Aroor AR, Mandavia CH, Sowers JR. Insulin resistance and heart failure: molecular mechanisms. Heart Fail Clin. 2012;8:609–17.
56. Shimizu I, Minamino T, Toko H, Okada S, Ikeda H, Yasuda N, Tateno K, Moriya J, Yokoyama M, Nojima A, et al. Excessive cardiac insulin signaling exacerbates systolic dysfunction induced by pressure overload in rodents. J Clin Invest. 2010;120:1506–14.
57. Riehle C, Weatherford ET, Wende AR, Jaishy BP, Seei AW, McCarty NS, Rech M, Shi Q, Reddy GR, Kutschke WJ, et al. Insulin receptor substrates differentially exacerbate insulin-mediated left ventricular remodeling. JCI Insight. 2020;5.
58. Alrob OA, Sankaralingam S, Ma C, Wagg CS, Fillmore N, Jaswal JS, Sack MN, Lehner R, Gupta MP, Michelakis ED, et al. Obesity-induced lysine acetylation increases cardiac fatty acid oxidation and impairs insulin signalling. Cardiovasc Res. 2014;103:485–97.
59. Masoud WG, Ussher JR, Wang W, Jaswal JS, Wagg CS, Dyck JR, Lygate CA, Neubauer S, Clanachan AS, Lopaschuk GD. Failing mouse hearts utilize energy inefficiently and benefit from improved coupling of glycolysis and glucose oxidation. Cardiovasc Res. 2014;101:30–8.
60. Ussher JR, Koves TR, Jaswal JS, Zhang L, Ilkayeva O, Dyck JR, Muoio DM, Lopaschuk GD. Insulin-stimulated cardiac glucose oxidation is increased in high-fat diet-induced obese mice lacking malonyl CoA decarboxylase. Diabetes. 2009;58:1766–75.
61. Buchanan J, Mazumder PK, Hu P, Chakrabarti G, Roberts MW, Yun UJ, Cooksey RC, Litwin SE, Abel ED. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. Endocrinology. 2005;146:5341–9.
62. Carley AN, Severson DL. Fatty acid metabolism is enhanced in type 2 diabetic hearts. Biochim Biophys Acta. 2005;1734:112–26.
63. Sung MM, Das SK, Levasseur J, Byrne NJ, Fung D, Kim T, Masson G, Boisvenue J, Soltys CL, Oudit GY, et al. Resveratrol treatment of mice with pressure overload-induced heart failure improves diastolic function and cardiac energy metabolism. Circ Heart Fail. 2014.
64. Sankaralingam S, Abo Alrob O, Zhang L, Jaswal JS, Wagg CS, Fukushima A, Padwal RS, Johnstone DE, Sharma AM, Lopaschuk GD. Lowering body weight in obese mice with diastolic heart failure improves cardiac insulin sensitivity and function: implications for the obesity paradox. Diabetes. 2015;64:1643–57.
65. Jackson RH, Singer TP. Inactivation of the 2-ketoglutarate and pyruvate dehydrogenase complexes of beef heart by branched chain keto acids. J Biol Chem. 1983;258:1857–65.
66. Walejko JM, Christopher BA, Crown SB, Zhang GF, Pickar-Oliver A, Yoneshiro T, Foster MW, Page S, van Vliet S, Ilkayeva O, et al. Branched-chain alpha-ketoacids are preferentially reaminated and activate protein synthesis in the heart. Nat Commun. 2021;12:1680.
67. Bertrand SM, Ancellin N, Beaufils B, Bingham RP, Borthwick JA, Boullay AB, Boursier E, Carter PS, Chung CW, Churcher I, et al. The discovery of in vivo active mitochondrial branched-chain aminotransferase (BCATm) inhibitors by hybridizing fragment and HTS hits. J Med Chem. 2015;58:7140–63.
68. Tso SC, Gui WJ, Wu CY, Chuang JL, Qi X, Skvora KJ, Dork K, Wallace AL, Morlock LK, Lee BH, et al. Benzothiophene carboxylate derivatives as novel allosteric inhibitors of branched-chain alpha-ketoacid dehydrogenase kinase. J Biol Chem. 2014;289:20583–93.
69. Chen M, Gao C, Yu J, Ren S, Wang M, Wynn RM, Chuang DT, Wang Y, Sun H. Therapeutic effect of targeting branched-chain amino acid catabolic flux in pressure-overload induced heart failure. J Am Heart Assoc. 2019;8:e011625.
70. McGarrah RW, Zhang GF, Christopher BA, Deleye Y, Walejko JM, Page S, Ilkayeva O, White PJ, Newgard CB. Dietary branched-chain amino acid restriction alters fuel selection and reduces triglyceride stores in hearts of Zucker fatty rats. Am J Physiol Endocrinol Metab. 2020;318:E216-E223.
71. Jachthuber Trub C, Balikcioglu M, Freemark M, Bain J, Muehlbauer M, Ilkayeva O, White PJ, Armstrong S, Ostbye T, Grambow S, et al. Impact of lifestyle Intervention on branched-chain amino acid catabolism and insulin sensitivity in adolescents with obesity. Endocrinol Diabetes Metab. 2021;4:e00250.