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CrossTalk opposing view: Ketone bodies are not an important metabolic fuel for the heart

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While the heart is a ‘metabolic omnivore’, the predominant sources of energy production are fatty acid and glucose/lactate catabolism (Stanley *et al.* 2005). Cardiomyocytes can also utilize ketone bodies but circulating concentrations of ketones are typically low compared to other substrates in the fed state (Stanley *et al.* 2005). Regardless, studies of rodent isolated working hearts have suggested that even at normal physiological concentrations of mixed substrates, the perfused heart can derive a substantial amount (~34%) of acetyl-CoA from ketones (Stowe *et al.* 2006), and cardiac ketone utilization can be enhanced in proportion to delivery (Jeffrey *et al.* 1995). The two main ketone bodies, β-hydroxybutyrate (βOHB), and acetoacetate (AcAc), are catabolized by two mitochondrial enzymes, β-hydroxybutyrate dehydrogenase 1 (BDH1) and succinyl-CoA:3-oxoacid CoA transferase (SCOT), respectively. A great deal of excitement has been drawn to cardiac ketone metabolism due to recent evidence demonstrating that failing mouse and human hearts preferentially switch to ketone utilization (Aubert *et al.* 2016; Bedi *et al.* 2016). Ketone extraction and oxidation are increased in failing human hearts compared to normal hearts (Monzo *et al.* 2020; Murashige *et al.* 2020). The following discussion describes a parallel body of work indicating that ketones may not be sufficient to sustain the metabolic demand of the heart and raises the debate regarding the importance of ketones as a metabolic fuel.

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Author contributions

All authors conceived, wrote, and edited this manuscript. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Additional information

Competing interests

None.

Ketone metabolism insights from *ex vivo* studies

Cardiac ketone metabolism has been studied extensively in isolated hearts, where the heart is isolated and perfused with buffer containing metabolite(s). Early work suggested that ketones could serve as the preferred oxidative fuel in Langendorff-perfused rat hearts (Williamson & Krebs, 1961). However, using an isolated working heart model, Taegtmeyer and colleagues demonstrated that ketone oxidation rates were unchanged in response to increased workload (Taegtmeyer *et al.* 1980). Also, perfusion of ketones as the sole metabolic substrate could not sustain cardiac work (Taegtmeyer *et al.* 1980). Only if the hearts were perfused with a combination of ketone and glucose (Taegtmeyer *et al.* 1980), or ketone and fatty acid (Russell *et al.* 1995) could contractile work be maintained. The authors described that hearts perfused with AcAc alone displayed inhibition of 2-oxoglutarate dehydrogenase activity due to sequestration of free CoA (Taegtmeyer, 1983; Russell & Taegtmeyer, 1991). This contractile dysfunction and loss of free CoA was reversed by addition of glucose, fatty-acylcarnitine or TCA cycle intermediates to the perfusate. A more recent study demonstrated that isolated normal working hearts and isolated pressure-overload failing hearts perfused with βOHB increased overall ATP production due to enhanced ketone and glucose utilization, but cardiac efficiency was unchanged (Ho *et al.* 2019).

A recent study in *The Journal of Physiology* also supports the notion of ketones not being an important metabolic fuel for cardiac mitochondrial oxidation *ex vivo*. Petrick and colleagues demonstrated that when AcAc or βOHB was added to mitochondria isolated from left ventricle or permeabilized left ventricular muscle fibres, the maximal mitochondrial respiration from ketones was low compared to pyruvate (Petrick *et al.* 2020). Additionally, if pyruvate was already present in these preparations, addition of ketones could not further increase mitochondrial respiration (Petrick *et al.* 2020). Thus, this study also suggests that ketones may not be an important metabolic fuel for the heart; however, the effects of ketones likely go beyond their metabolic role (Poffe & Hespel, 2020). For instance, ketones are known to have both signalling and post-translational modification/epigenetic roles (Puchalska & Crawford, 2017).

Ketones and substrate competition

While the heart is metabolically flexible, all substrates are catabolized to acetyl-CoA for oxidation. Several studies suggest that ketones compete with glucose and fatty acids as metabolic fuel. Both *in vitro* and *in vivo* studies have shown that ketones compete with fatty acids and inhibit their oxidation (Hasselbaink *et al.* 2003; Stanley *et al.* 2003). It has also been demonstrated that chronic exposure to βOHB induces insulin resistance in isolated cardiomyocytes (Tardif *et al.* 2001; Pelletier *et al.* 2007). βOHB infusion can also reduce cardiac glucose uptake in humans (Gormsen *et al.* 2017) suggesting that ketones have the potential to compete with both glucose uptake and oxidation in the heart. However, the ketone-associated inhibition of fat or glucose oxidation appears to be specific to ketone body concentration, with lower ketone concentrations either not affecting, or even enhancing cardiac oxidative capacity of these other substrates (Ho *et al.* 2019).

Insights from *in vivo* studies on myocardial ketone metabolism

While *ex vivo* studies allow direct assessment of myocardial substrate metabolism, these interpretations of cardiac fuel utilization may not faithfully represent the *in vivo* scenario, particularly in conditions associated with chronically elevated ketone levels such as fasting, consumption of a ketogenic diet, or uncontrolled diabetes. Intriguingly, high ketogenic conditions have been shown to diminish the ability of the heart to catabolize ketone bodies. Hearts from mice provided a ketogenic diet or after 24 h fasting displayed reduced expression of ketolytic enzymes, and reduced ketone oxidation both *in vivo* and *ex vivo* (Wentz *et al.* 2010). We and others have also described decreased cardiac expression of BDH1 and SCOT after ketogenic diet or fasting, even in failing hearts that were previously upregulating the expression of these ketolytic enzymes (McCommis *et al.* 2020; Zhang *et al.* 2020). We also reported a similar observation in a mouse model of diabetes, where despite elevated levels of circulating ketone bodies, myocardial ketolytic machinery was inhibited (Brahma *et al.* 2020). During these physiological and pathological states of high ketosis, the heart is also receiving high levels of fatty acids delivered either from dietary sources with the ketogenic diet or from enhanced adipose tissue lipolysis during any of these scenarios. Thus, it appears the heart may be downregulating ketolytic machinery in order to maintain or enhance fatty acid oxidation during ketosis (Wentz *et al.* 2010; McCommis *et al.* 2020). Interestingly, enhanced cardiac glucose uptake and utilization from glucose transporter-1 or −4 overexpression is also able to downregulate ketolytic enzyme expression and decrease ketone oxidation (Yan *et al.* 2009; Brahma *et al.* 2020). Altogether, these findings suggest that in chronic ketotic states *in vivo*, hearts downregulate the ketolytic enzymes and preferentially oxidize other substrates.

Lastly, several genetic mouse models also suggest that ketone metabolism is not crucial to maintaining normal cardiac homeostasis (Schugar *et al.* 2014; Horton *et al.* 2019). As described in these studies, mice with cardiac deletion of SCOT (Schugar *et al.* 2014) or BDH1 (Horton *et al.* 2019), which cannot metabolize ketone bodies, display normal cardiac size and function, unless subjected to pressure overload when both models display enhanced cardiac remodelling and dysfunction. Thus, complete genetic loss of the cardiac ketolytic machinery does not negatively affect cardiac performance in the absence of a secondary stress.

Conclusions

In our opinion, controversies related to the importance of cardiac ketone metabolism may be due to comparing acute *ex vivo* studies to the chronic *in vivo* scenario. Additionally, some findings appear to be different between studies comparing high, but submillimolar, to very high millimolar levels of ketones. But we believe the bulk of evidence from *in vitro* and *in vivo* experimentation suggests that ketone catabolism is not crucial for normal hearts. Further understanding is needed to address the importance of ketone metabolism in heart failure, as recent studies in preclinical models (Ho *et al.* 2019; Horton *et al.* 2019; Yurista *et al.* 2021) and humans (Bedi *et al.* 2016; Monzo *et al.* 2020; Murashige *et al.* 2020) suggest enhanced ketone body metabolism in heart failure.

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Biography

Manoja Kumar Brahma is a postdoctoral fellow in the Signal Transduction and Metabolism Laboratory at the Université libre de Bruxelles (Belgium). He completed his PhD from the University of Graz at Austria followed by postdoctoral training in the laboratory of Dr Adam R. Wende at the University of Alabama at Birmingham (USA). His work was primarily focused on understanding why diabetic patients are susceptible to developing heart failure with a focus on defective myocardial ketone body metabolism.

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