The Journal of Physiology

CROSSTALK

Rebuttal from Gary D. Lopaschuk and Qutuba G. Karwi

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

[1]*Cardiovascular Research Centre, University of Alberta, Edmonton, Alberta, Canada*

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

Email: karwi@ualberta.ca

Edited by: Francisco Sepúlveda & Yasuhiko Minokoshi

Linked articles: This article is part of a CrossTalk debate. Click the links to read the other articles in this debate: https://doi.org/10.1113/JP281005, https://doi.org/10.1113/JP281004, https://doi.org/10.1113/JP281453.

The Cross-talk article by Brahma *et al* suggests that ketone bodies are not an important fuel for the heart. However, the authors acknowledge a study in which ketone oxidation contributed 34% of the total ATP production in the heart, even when the heart is exposed to low levels of ketone (~0.28 mM) (Stowe *et al.* 2006). This study concluded that 'ketones are the preferred substrate for energy production in the normal mouse heart *in vivo*'. Moreover, a recent study from our group has shown that ketone can become the major source of acetyl-CoA supply for the TCA cycle when its delivery to the heart is augmented (Ho *et al.* 2021). Furthermore, even when fatty acid levels are increased, ketone remains the major fuel source for the heart when ketone delivery to the heart is increased (Ho *et al.* 2021). Combined, we believe this demonstrates the importance of ketone bodies as fuel to the heart.

The article by Brahma *et al.* questions the interpretations of cardiac fuel utilization based on *ex vivo* models, suggesting that these interpretations may not faithfully represent the *in vivo* scenario. They justify this criticism based on the observation that cardiac ketone oxidation machinery is down-regulated *in vivo* under conditions associated with chronically elevated ketone levels, such as fasting, consumption of a ketogenic diet or uncontrolled diabetes. While it is not unexpected that chronic exposure of the heart to high levels of ketones might down-regulate ketone oxidation enzymes, it does not necessarily mean that ketone oxidation rates decrease under these conditions. Any potential decrease in ketone oxidation rates due to decreased ketone oxidative enzyme expression may be compensated for by the increase in ketone concentration to which the heart is exposed. Indeed, increasing the concentration of ketone to which the heart is exposed does dramatically increase ketone oxidation rates (Ho *et al.* 2021).

Part of the conclusion that ketones are not an important fuel for the heart is based on the observation that cardiac-specific deletion of either BDH1 or SCOT, two key enzymes involved in ketone oxidation, is not associated with significant alterations in cardiac size or function (Schugar *et al.* 2014; Horton *et al.* 2019). However, if mice with a cardiac deletion of either of these enzymes are subjected to stress, they do show aggravated cardiac dysfunction and adverse remodelling (Schugar *et al.* 2014; Horton *et al.* 2019). This suggests that ketone oxidation is indeed important in preventing this from occurring.

In conclusion, we propose that ketone is an important fuel source for the heart. In addition, increasing ketone oxidation may represent a new therapeutic approach to enhance cardiac energy metabolism and to treat heart failure.

Call for comments

Readers are invited to give their views on this and the accompanying CrossTalk articles in this issue by submitting a brief (250 word) comment. Comments may be submitted up to 6 weeks after publication of the article, at which point the discussion will close and the CrossTalk authors will be invited to submit a 'LastWord'. Please email your comment, including a title and a declaration of interest, to jphysiol@physoc.org. Comments will be moderated and accepted comments will be published online only as 'supporting information' to the original debate articles once discussion has closed.

References

Ho KL, Karwi QG, Wagg C, Zhang L, Vo K, Altamimi T, Uddin GM, Ussher JR & Lopaschuk GD (2021). Ketones can become the major fuel source for the heart but do not increase cardiac efficiency. *Cardiovasc Res* (in press), doi: 10.1093/cvr/cvaa143.

Horton JL, Davidson MT, Kurishima C, Vega RB, Powers JC, Matsuura TR, Petucci C, Lewandowski ED, Crawford PA, Muoio DM, Recchia FA & Kelly DP (2019). The failing heart utilizes 3-hydroxybutyrate as a metabolic stress defense. *JCI Insight* **4**, e124079.

Schugar RC, Moll AR, Andre d'Avignon D, Weinheimer CJ, Kovacs A & Crawford PA (2014). Cardiomyocyte-specific deficiency of ketone body metabolism promotes accelerated pathological remodeling. *Mol Metab* **3**, 754–769.

Stowe KA, Burgess SC, Merritt M, Sherry AD & Malloy CR (2006). Storage and oxidation of long-chain fatty acids in the C57/BL6 mouse heart as measured by NMR spectroscopy. *FEBS Lett* **580**, 4282–4287.

Additional information

Competing interests

None.

Author contributions

Both 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.

Funding

This work was supported by a Canadian Institute for Health Research Foundation Grant to G.D.L., and an Alberta Innovates Postgraduate Fellowship in Health Innovation to Q.G.K.

Keywords

cardiac efficiency, heart failure, ketone oxidation

DOI: 10.1113/JP281452