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CROSSTALK

Rebuttal from Lasse K. Bak and Anne B. Walls

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Just to be clear in advance, we are not as such arguing that lactate is not metabolised by neurons or that access to lactate is not somehow important for neuron-driven processes such as memory formation. However, we are not convinced that activity-dependent, unidirectional shuttling of lactate from astrocytes to neurons is a fundamental process in the brain. As we have argued, conventional biochemical knowledge dictates that lactate can and will be produced and consumed in both neurons and astrocytes. In their arguments for an important unidirectional flow of lactate Barros and Weber (2018) cite numerous studies whose results are not inconsistent with the existence of such a shuttle *per se*, but also do not provide unequivocal, direct evidence in favour of unidirectional shuttling. In keeping with our original counterarguments, we will again point to (1) the fact that neurons do indeed increase their uptake and metabolism of extracellular glucose during activation even in the presence of physiological levels of lactate), and (2) that there is nothing in the biochemical design of neurons or astrocytes to suggest that astrocytes are able to outpace neurons in terms of production of lactate during activation. Both cell types express lactate dehydrogenase and thus any production of pyruvate will result in production, and possible release, of lactate due to simple mass action. As we have argued, only mass action can push the pyruvate/lactate equilibrium towards pyruvate in neurons, i.e. astrocytes need to significantly outpace neurons in glycolytic activity and lactate production to establish a unidirectional flux. In our opinion, any eventual *in situ* evidence will need to propose a model to account for the biochemical mechanisms responsible, i.e. what is it that makes the astrocytic glycolytic machinery outpace neurons during activation? A related pertinent question is how astrocytes, if during activation they are only producing pyruvate/lactate for export and not for oxidative metabolism, can maintain their own energy requirements? Finally, as pointed out by Dr Dienel in several original publications and reviews not mentioned by Barros and Weber, the lactate produced during activation seems to be dispersed within the brain tissue following activation rather than being metabolised locally, as would be expected from the lactate shuttle hypothesis (e.g. as detailed in this recent review: Dienel, 2017). Thus, we still do not find ourselves convinced by the arguments proposed by Barros and Weber that any flow of lactate is unidirectional from astrocytes to neurons.

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Additional information

Competing interests

None declared.

Author contributions

Both authors have contributed to the conception or design of the work and drafting the work or revising it critically for important intellectual content. Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

The following supporting information is available in the online version of this article.

Comments.
Last words by Barros & Weber.
Last words by Bak & Walls.

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