nature portfolio

Peer Review File

Reviewers' Comments:

Reviewer #1:
Remarks to the Author:
This version of the manuscript by Fernandez-Moncada et al is considerably improved. The message is much clearer and the discussion well balanced.

This is the result of a fair review process: to critically assess the manuscript and suggest ways to improve it. In this context I was a bit surprised by the dismissive replies that the authors provided to some of the questions I raised: my intention when reviewing manuscripts is to provide my best effort to suggest possible improvements. I would have expected a more collegial reaction given the number of senior authors.

This is now a good article with a clear message; it is however not a seminal article as the effects of lactate on synaptic transmission have already been described in the very nice article (definitely seminal in this case) by Jimenez-Blasco, Nature, 2020, as well as by other groups. This is why I still think that the article would gain in tackling the molecular signaling mechanisms of the observed effects, in particular regarding the HCAR1-mediated metabolic effect. Many questions remain open, as ably discussed by the authors, in particular regarding the relevance of the findings reported for pharmacological effects of cannabinoids in humans (clearly not improving cognition) or the effects of HCAR1 receptor activation (essentially inhibitory and not excitatory).

But at the end it is up to the authors to decide whether to publish a good paper that will add some body of information to the field or an exceptional one that will leave a mark.

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We thank the Reviewer for the nice comments on our work.