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CORRESPONDENCE

Comment on report of a large reduction in cortical GABA following ketone ingestion

Neuropsychopharmacology (2023) 48:847; https://doi.org/10.1038/s41386-022-01511-1

The recent article by Hone-Blanchet et al. [1] reports substantial reductions in both GABA and glutamate concentrations following ingestion of a ketone ester known to elevate D-beta-hydroxybutyrate (D-βHB) levels. A striking aspect of their results is that GABA levels appeared to fall by roughly 50% over 30 min following ketone ingestion. This is such a large reduction that it raises the question of whether it is physiologically plausible, especially given that there is no mention of adverse cognitive or functional consequences of this change. It is essential to exclude the possibility that these findings might be contaminated by measurement error.

One indication of possible measurement error is the unusually high coefficient of variation (CV) of pre-ingestion GABA values. As calculated from Figures 2A, 2B, 2G, and 2H, the CV values range from 17% to 47%, with an average of 28%. Supplemental Tables 1 and 3 indicate an even higher average CV of 34% for pre-ingestion GABA. Similarly, Figures 2A and 2B portray baseline GABA levels as varying over a three- to four-fold range, which is not physiologically credible in healthy adults. In contrast, a large multi-site study reported average within-site CVs of 9.5% and 18.8% for edited GABA+ and macromolecule-suppressed GABA respectively [2]. The GABA values reported by Hone-Blanchet et al. are estimated from spectra acquired with a STEAM sequence and appear to include a relatively high degree of noise variance.

LCModel estimates of GABA from spectra acquired without editing may be both noisy and sensitive to changes in how the spectral baseline and macromolecular signals are estimated. D-βHB resonances include a methyl doublet near 1.2 ppm and a methylene multiplet with peaks near 2.3 and 2.4 ppm [3, 4]. The former doublet peak overlaps a prominent macromolecular resonance, while the latter multiplet peaks are close to both GABA and glutamate resonances. Even with D-βHB included in the basis set, the added presence of these resonances in the spectra following ketone ingestion could systematically alter how LCModel estimates the macromolecular signals or the underlying spectral baseline. If this occurred, it could produce artifactual reductions in the GABA estimates.

If we are to believe a ~50% drop in GABA without functional consequences, some form of additional validation would be helpful, especially given higher than usual variance in the GABA estimates. For example, if pre- and post-ketone ingestion spectra are frequency-aligned, amplitude-scaled, and averaged across subjects, a clear residual GABA resonance at 3.0 ppm should be evident in the grand mean difference spectrum (pre minus post). For the posterior voxel experiment, comparing this residual GABA signal in individual subjects' difference spectra in the ketone and glucose conditions could provide independent confirmation of a large reduction in GABA following ketone ingestion.

Studies of the neurometabolic effects of ketones have important theoretical and clinical implications. The authors' article may influence how future research resources are allocated in pursuing these important questions. It is essential to exclude the possibility that measurement error has contaminated their claim of large reductions in cortical GABA following ketone ingestion.

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REFERENCES

1. Hone-Blanchet A, Antal B, McMahon L, Lithen A, Smith NA, Stufflebeam S, et al. Acute administration of ketone beta-hydroxybutyrate downregulates 7T proton magnetic resonance spectroscopy-derived levels of anterior and posterior cingulate GABA and glutamate in healthy adults. Neuropsychopharmacology. 2022. https://doi.org/10.1038/s41386-022-01364-8.
2. Mikkelsen M, Barker PB, Bhattacharyya PK, Brix MK, Buur PF, Cecil KM, et al. Big GABA: Edited MR spectroscopy at 24 research sites. Neuroimage 2017;159:32–45. https://doi.org/10.1016/j.neuroimage.2017.07.021.
3. Cecil KM, Mulkey SB, Ou X, Glasier CM. Brain ketones detected by proton magnetic resonance spectroscopy in an infant with Ohtahara syndrome treated with ketogenic diet. Pediatr Radiol. 2015;45:133–7.
4. de Graaf RA. In vivo NMR spectroscopy: principles and techniques. 3rd ed. Hoboken, NJ: Wiley; 2019.

AUTHOR CONTRIBUTIONS

RJM is responsible for all aspects of this letter.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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Received: 9 September 2022 Revised: 4 November 2022 Accepted: 8 November 2022
Published online: 28 November 2022