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Peer Review

Review of: "The KHK–Polyol Axis as a Convergent Energetic Bottleneck in Chronic Disease Persistence"

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The present manuscript suggests a comprehensive metabolic model in which the metabolism of fructose through ketohexokinase (KHK) serves as a key energetic pathway. This pathway transforms various stress factors into a continuous, self-sustaining energetic shortage that hinders cellular repair and encourages the development of chronic diseases. The model highlights the reduction of the adenylate pool, fragmentation of mitochondria, and depletion of NAD^+ as key mechanisms that contribute to energetic hysteresis and a prolonged Cell Danger Response.

The manuscript addresses an interesting point but with several limitations. First, the manuscript does not state clearly enough what type of publication it is. I cannot consider it as a classic review nor a meta-analysis. Although I really liked the type of narrative used, the language goes beyond evidence and becomes merely narrative-causal. Indeed, the manuscript proposes a systems-level energetic constraint model, but causal language is used more than evidence-based language. For sure, the authors integrate disparate observations (i.e., fructose metabolism, mitochondrial dynamics, NAD^+ depletion, and chronic disease persistence) into a coherent mechanistic narrative. This is a notable strength, but: 1) the model's reliance on sustained adenylate pool depletion in adult tissues in vivo is insufficiently supported by direct experimental evidence; 2) the role attributed to endogenous fructose metabolism in energy-sensing neurons lacks quantitative validation, particularly given neuronal buffering capacity and the kinetic properties of KHK-A; 3) it remains unclear whether KHK-mediated fructose metabolism is necessary and sufficient to stabilize mitochondrial fragmentation, or whether it operates alongside parallel stress-response pathways.

Those points represent a critical empirical gap.

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Overall, this manuscript presents a compelling and original metabolic framework with significant “heuristic” and hypothesis-generating value. However, its impact would be strengthened by quantitative in vivo evidence and a more explicit delineation of contexts in which the model is expected to apply.

If it is not possible to conduct ″actual″ tests, it would be sufficient to modify the language and submit the article in the most suitable format (not a simple review article but a theoretical one). The metaphors used (like “phosphate heist,” “dead battery,” “shredder,” “forest fire,” “voltage spike”...) are very powerful from a descriptive point of view, but perhaps there are too many of them. Similarly, some phrases are more rhetorical than analytical (“The real problem is a physical hole in the battery cell”) and some concepts are redundant (like energetic hysteresis).

I repeat, if this were solely a matter of scientific dissemination, I can say that I really liked the style used, but I do not think that is the ultimate purpose of this publication. For this reason, to sum up, the manuscript presents an ambitious and internally coherent systems-level hypothesis with strong heuristic value. However, the authors should (i) further constrain causal language, (ii) clarify the epistemic status of speculative components (particularly regarding cerebral polyol flux), and (iii) moderate metaphorical framing to align with a review format. With these revisions, the work would represent a valuable conceptual contribution to metabolic systems biology.

Declarations

Potential competing interests: No potential competing interests to declare.