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Peer Review

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

Torsak Tippairote[1]

1. Independent researcher

This manuscript presents an ambitious and integrative systems-level hypothesis positioning the KHK–polyol axis as a convergent energetic bottleneck underlying chronic disease persistence. The conceptual synthesis linking unregulated fructose phosphorylation, adenylate pool contraction, mitochondrial fission, CD38-mediated NAD^+ depletion, and hypothalamic “endocrine triage” is intellectually compelling and clearly articulated. The tiered confidence framework and explicit falsifiable predictions are strengths and enhance the manuscript’s scientific rigor.

However, several mechanistic transitions require tighter clarification. In particular, the treatment of AMP as primarily a driver of AMPD-mediated adenylate loss underplays its established role in activating AMPK and increasing mitochondrial oxidative throughput. The manuscript would benefit from clearer delineation of the quantitative or kinetic conditions under which AMP signaling shifts from adaptive (AMPK-dominant) to degradative (AMPD-dominant). Without this threshold definition, the central claim of structural adenylate contraction as a stabilizing mechanism risks overgeneralization beyond high-flux fructose-loading contexts.

Additionally, while individual biochemical nodes are well supported, the proposed systemic propagation model (“contagious fragility”) and hypothalamic fail-point hypothesis remain speculative and should be framed more cautiously to avoid causal overextension.

Overall, this is a provocative and potentially high-impact theoretical framework. Strengthening the quantitative boundaries of the AMP branch-point logic and clearly distinguishing established mechanisms from integrative extrapolation would substantially improve its translational credibility.

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Declarations

Potential competing interests: No potential competing interests to declare.