Review of: "Reduced Blood to Brain Glucose Transport as The Cause For Hyperglycemia: a Model That Resolves Multiple Anomalies in Type 2 Diabetes"

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Potential competing interests: No potential competing interests to declare.

Ohja and Watve call attention to the likelihood that systemic insulin resistance is not the root cause of hyperglycemia in type 2 diabetes (T2D). They consider an appealing alternate hypothesis that reduced glucose transport to the brain is the cause of hyperglycemia in T2D. Yet, their presentation is flawed in many respects itemized below. Despite the amount of information they present, they do not provide a focused explanation for their new perspective on hyperglycemia in T2D. Indeed, much of their lengthy introduction (through section 1.3) reads more like rough notes for an introduction than professional text ready for submission. Far more serious, however, is the lack of mathematical explanations (or citations providing that) for the equations in their novel model and the absence of animal experiments validating the utility and predictions of their model.

INTRODUCTION

1. In the first sentence of the Introduction, the authors could give a more accurate characterization of type 2 diabetes (T2D) with the assistance of the review by DeFronzo et al. (2015) which they cite. As written, the sentence implies that T2D is a metabolic disorder defined by hyperglycemia and insulin resistance even though insulin resistance is not a diagnostic criterion for the disorder (see the American Diabetes Association 2022 Classification and Diagnosis of Diabetes [Diabetes Care 45, suppl. 1, 2022]). It would be more accurate to say T2D is a metabolic disorder that is distinguished from other types of diabetes by the combination of hyperglycemia often occurring in association with systemic insulin resistance.
2. Provide an epidemiological reference for the statement that T2D accounts for all diabetes cases.
3. The progression of historical events mentioned in the first paragraph needs to be clarified and focused. What kind of non-lethal damage to the fourth ventricle reported by Claude Bernard caused what kind of impairment to homeostatic control? In what type of experiments did Frederick Banting find that pancreatic extracts lowered blood glucose? The sentence beginning, “It is necessary to note” is not necessary where stated and should be eliminated. So should the first clause of the sentence beginning, “The distinction between type 1 and type 2 diabetes … .” That sentence should be edited to read, “It was not until [give date and reference] that insulin deficiency was not the primary cause of hyperglycemia in type 2 diabetes.” The unreferenced and conjectural assertion expressed in the last sentence of the first paragraph should be cut. Such judgmental statements detract from the argument being made, which should be limited to findings and conclusions identified in the literature and cited by the authors.

4. The second paragraph of the Introduction begins with the word, “Furthermore”, which is a non-specific connective that leaves unstated the idea connecting the paragraph with the preceding one. The sentence suggests that the connection is to the “insulin hypothesis,” presumably the unstated idea that insulin resistance is the cause of hyperglycemia in T2D. This reflects a lack of coherence in the Introduction, which needs to more succinctly written so that one point leads logically to the next without interruption by secondary issues. It should all lead to an explicit statement of the main reason for the present study and how it will be approached.
5. Yes, there is a means of measuring insulin resistance independent of its affects on glucose uptake, which the authors acknowledge in passing. The gold standard for measuring insulin resistance is actually its ability to activate the insulin receptor regardless of any consequent effect on glucose uptake. So the point that the authors should be making is not the circularity of the insulin resistance hypothesis, but the failure they note that direct impairment of insulin signaling does “not alter fasting glucose in the expected direction.”
6. The sentence beginning on line 83 and ending on line 85 is confusing.
7. The sentence on line 103 should read, “The following is a list of empirical patterns with which a glucose homeostasis model needs to be consistent.” The beginning of each item in the list needs have the same structure for linguistic consistency. Suggested solutions to this problem are given below.
8. The beginning of line 104 should read, ”Steady state fasting glucose.” That should followed by the statement that, “There is adequate evidence that fasting glucose is a steady state.”
9. The beginning of line 110 should read, “Stable, steady-state fasting insulin.”
10. The beginning of line 113 should read, “Normoglycemia with hyperinsulinemia in the prediabetic state.”
11. The beginning of line 132 should read, “Hyperinsulinemia preceding insulin resistance and T2DM”.
12. The beginning of line 140 should read, “Explanations of features in impaired glucose tolerance curves, including the post-meal glucose curves and alterations in prediabetic and diabetic states”.
13. The beginning of line 147 should read, “The relationship of normal fasting glucose to impaired glucose tolerance (NFG-IGT”.
14. The beginning of line 150 should read. “The effect of stress on hyperglycemia”.
15. The beginning of line 153 should read, “The effect of intensive exercise on hyperglycemia”.
16. The beginning of line 158 should read, “The relationship between normal fasting glucose and post-glucose loads in knockout if the insulin receptor in specific tissues (skeletal muscle, fat, and liver)”.
17. The beginning of line 168 should read, “Reduced glucose transport to the brain in obese and prediabetic individuals”.
18. The beginning of line 177 should read, “T2DM=specific islet amyloid deposition”.
19. The beginning of line 182 should read, “The pattern of B cell degeneration in T2DM”.
20. The beginning of line 188 should read, “The relationship of SGLT2 inhibitors to liver glucose production and ketogenesis”.
21. The beginning of line 198 should read, “Hyperglycemia associated with bacterial meningitis.”
22. The sentence starting on line 202 should read, “The good correlation between postmeal glucose and insulin but the poor correlation between FG and FI (Diwekar-Joshi & Watve, 2020) in population data”.
23. The sentence starting on line 204 should read, “The poor correlation of FG and FI in prediabetes, but the strong

correlation of HOMA-B and HOMA-IR (Diwekar-Joshi & Watve, 2020) in population data."

24. The sentences starting on line 207 and line 216 should begin with "The".
25. "Our expectation from a satisfactory model" is awkward. The sentence is better written as follows: "A satisfactory model in our opinion should predict all the phenomena noted above."
26. The beginning of the sentence on line 230 is better written as, "There is a long history of mathematical models of glucose homeostasis and of the origin and progression of T1D and T2D."
27. The authors have to purge their manuscript of terms expressing exasperation over perceived inadequacies of earlier investigators exemplified in lines 232-235. The criticism can be made simply by pointing out what those inadequacies are in a neutral fashion. This neutral approach is more to the point and will be more readily accepted by readers than language which shows contempt for earlier investigators who may not have made what the present authors consider errors for the reasons they think.
28. The first paragraph of the section on peripheral models of glucose homeostasis is essentially an assertion that none of the models proposed to date meet the criteria the authors listed as necessary for glucose homeostasis models earlier in their commentary. For the most part, however, it is limited almost entirely to general assertions with only limited mention of specific inadequacies of the models in question.
29. The author's model implicitly assumes that insulin in the brain is derived almost exclusively from the pancreas, but there is abundant evidence that that even the adult brain synthesizes insulin and that the amount is not minor compared to pancreatic insulin in the brain (J. Havrankova et al., PNAS 75: 5737-5741, 1978, D. LeRoith et al., Advances in Metabolic Disorders 10: 303-340, 1983, E.A. Csajbok and G. Tamas, Diabetologia 59: 1609-1615, 2016, T. Dakic et al., J. Molecular Sciences 24: 6586, 2023).
30. Why do the authors not take into account direct brain intake of insulin, which occurs via insulin transporters independent of endothelial insulin receptors (E.M. Rhea et al., Experimental Neurology 313: 10-15, 2019)?
31. What is the basis for the values of the parameters used in Table 1?
32. What are the sources or derivations of the equations in the authors' novel model?
33. Why is no data presented from animal experiments to validate the new model and simulations performed with it?
34. Without answers to the questions just asked, this reviewer lacks the context within which to review the Results or Discussion of this manuscript.