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.

The manuscript presents an innovative approach to the pathogenesis of type 2 diabetes, challenging conventional insulin resistance theories and proposing a model centered on brain glucose homeostasis. The authors provide a thorough analysis of empirical patterns and anomalies related to type 2 diabetes, supporting their hypothesis with a robust mathematical and conceptual framework. Below, I present my suggestions and queries for further clarification and enhancement of the work.

Major Points:

1. The authors argue against traditional models. Could they provide a more detailed discussion on how their model addresses the anomalies that these models cannot explain?
2. While the approach is novel, it would be beneficial to include more direct experimental evidence supporting this model. Are there ongoing or planned studies that could empirically validate this hypothesis?
3. Could the authors expand on how specifically these factors affect the expression of glucose transporters and vascular function in their model?
4. A more detailed comparison between the proposed model and classical models would be useful, particularly in terms of therapeutic implications and management of type 2 diabetes.

Minor Points:

1. What are the specific methodologies employed in the studies cited to support their hypothesis? Are there limitations in these methodologies that might affect the interpretation of the results?
2. Based on your model, what would be the potential therapeutic strategies? How might these differ from current strategies based on insulin resistance theory?
3. Although the mathematical model provides a solid theoretical basis, discussing how it could be simplified or adapted for application in clinical research and medical practice would be beneficial.

Points for reflection:

1. The manuscript suggests that evidence is accumulating against insulin resistance models, citing the absence of lasting hyperglycemia in insulin receptor knockouts and the perplexing state of hyperinsulinemic normoglycemia. This

contradicts established models where insulin resistance plays a central role in type 2 diabetes. How do the authors reconcile these findings with the substantial body of research supporting the insulin resistance hypothesis, especially considering the clinical effectiveness of treatments targeting insulin resistance?

2. The manuscript criticizes the insulin resistance hypothesis for its circular logic, stating that insulin resistance is measured by the inability of insulin to regulate glucose, which is also the definition of insulin resistance itself. Given that insulin resistance is a widely accepted concept in the pathophysiology of type 2 diabetes, can the authors provide concrete evidence or alternative methodologies that can independently measure insulin resistance, thus breaking this alleged circular logic?
3. The authors propose a model examining various factors like insulin resistance, β cell dysfunction, reduced rates of diffusion across the blood-brain barrier (BBB), and others. Considering the complexity and interplay of these factors in T2DM pathogenesis, how does the proposed model account for the multifactorial nature of T2DM, especially in light of current evidence supporting the interdependence of these factors in disease progression?

This manuscript represents a comprehensive analysis of the role of brain glucose homeostasis in type 2 diabetes. The depth of literature review and the insightful connections made between genetic markers and environmental factors provide a solid foundation for the study's assertions. However, to fully realize the potential of the manuscript for a high-impact publication, a series of significant revisions are required. I recommend a detailed response to each of the suggestions and questions raised, addressing them systematically in a point-by-point format. This will not only strengthen the arguments but also enhance the manuscript's clarity and academic rigor. I look forward to seeing the revised manuscript with the necessary amendments that reflect the responses to the points discussed.