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 work by Akanksha Ojha and Milind Watve entitled “Reduced Blood to Brain Glucose Transport as The Cause For Hyperglycemia: a Model That Resolves Multiple Anomalies in Type 2 Diabetes” reflects hard study and work done that has a lot of potential to impact the research field of Type 2 diabetes.

I have to say that, when I accepted to review this study, I did not realize that it was (only) about a mathematical model, which is not my expert field. For that, I apologize since my input will not have a great influence on improving your work.

Nevertheless, I have some minor considerations regarding the text itself:

- The text should be edited for English. Be careful with verb tenses. For example in the Introduction “(line 173) has been viewed as a response to hyperglycemia. However, Hwang et al. (2017) **show** that subnormal…” should be “**shown**”

- (line 182) 12. ‘**B** cell deterioration pattern: The deterioration of β cells…” I assumed that the**B** is in fact **β**

- I suggest that Bullets 16 and 17 come after Bullet 3

- Fig 1 is not properly formatted

- Figure 3 Legends are hard to read

Other comments:

In line 265 the authors said: “Plasma glucose levels are only a means to achieve the required supply of glucose to the brain. Since the transport of glucose to the brain is more restricted, when an adequate supply of glucose to the brain is ensured, it is likely that the supply to other organs is already ensured.” I would like the authors to discuss this sentence. One would expect that glucose levels in the brain must be primarily ensured since, and citing Ritter S. “the brain monitors glucose availability to ensure overall neurological function and survival” (Ritter S. Monitoring and Maintenance of Brain Glucose Supply: Importance of Hindbrain Catecholamine Neurons in This Multifaceted Task. https://www.ncbi.nlm.nih.gov/books/NBK453140/ doi: 10.1201/9781315120171-9).

Did the authors consider including gender-related differences in your model?

In this work, the authors developed a model that “predicts that glucose and insulin transportation to the brain has a major role in the development of diabetic symptoms compared to other peripheral changes. The blood-brain barrier vasculature, hence, may hold the key to understanding the shift from normal to diabetic condition”. This is quite interesting and my challenging question is if you considered developing a similar model that helps to understand the multifactorial neurodegenerative disease of Alzheimer (AD)? The connection between the occurrence of AD and type 2 diabetes is strong but poorly understood. Moreover, AD is the main cause of dementia which is also strongly related to vascular dysfunction.

Best regards and Happy holidays!

Ana Silva