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

Sangita Swapnasrita[1]

1 Maastricht University

Potential competing interests: No potential competing interests to declare.

The authors have done a targeted steady state model of glucose homeostasis in the brain with an underlying diabetes condition. As has been pointed out by the author, the most popular models are entangled in a loop, where proper model calibration is missing. The authors rightly note that, a model should not only validate some empirical solution, but must be correct in variety of scenarios. The involvement of brain signaling in glucose signaling has been suggested by many (theoretically). A quick google scholar search of “Role of brain in diabetes” gives the research outputs by Deem et al. 2017 (https://diabetesjournals.org/diabetes/article/66/7/1758/39993/How-Should-We-Think-About-the-Role-of-the-Brain-in) and Levin et al. 1999 (https://journals.physiology.org/doi/full/10.1152/ajpregu.1999.276.5.R1223) which are missing from the reference list.
I also believe that parts of the model equations are missing - refer to glucagon levels in Fig.3 but no mention of these equations have been made.

There are some other suggestions/critics (some necessary, some preferred):
1. Define G in equation 1, Kp, Ks in the iterative L determination and K4 determination

2. Kidney production and elimination of glucose is not discussed. This would be involved when discussing diabetes. Also an addition to equation 6.

3. Eq 10 does not make sense as K4 is the glucose-independent insulin secretion rate.

4. The authors state “This means that stress-induced hyperglycemia is unlikely to be seen in healthy individuals, while it is more likely in individuals with reduced vascular transport [7].” This is a very well-constructed argument.

5. The parameter values for K8 and K9 in Figure 1 c would explain the argument of hyperinsulinemic normoglycemic condition.

6. Explain Glucagon curves origin/model in Figure 3. Also add y-axis labels.

7. Check references thoroughly. For example, “John Thomas Sorensen, --by, Colton Thesis Supervisor, C. K., & Deen, W. M. (n.d.). *A PH’tSIOLOGIC MODEL OF GLUCOSE METABOLISM IN MAN AND ITS USE 1’0 DESIGN AND ASSESS IMPROVED INSULIN THERAPIES FOR DIABETES SUBMITTED TO THE DEPARTMENT OF*” is an incomplete

sentence.

8. Being a qualitative model, I assume many parameters are not explicitly experimentally derived. But cataloguing the used parameter values for each reasoning of the patterns might lead to discovery of consistent parameter sets that could potentially be correct parameter values (qualitatively).