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 publication of Akanksha and Watve presents an alternative theoretical model for hyperglycemia, that is based on glucose deprivation in the brain.

In the literature there is already a growing body of evidence that points to the fact, that brain hypometabolism precedes hyperglycemia.

Please cite new literature!

Impressive examples for brain-triggered hyperglycemia and increased hepatic glucose output come from treatment with antipsychotic drugs.

Please provide more general information in the introduction before you explain your model!

The metabolic demands of the brain amount to 20% of the body's overall energy consumption, although it makes only 3% of body mass. In addition, the brain has only modest energy reserves. Therefore the neurometabolism is highly dependent on a continuous supply of glucose from the systemic circulation. Glucose enters the brain through Glut1. The authors propose that vascular dysfunction is the main cause for brain hypometabolism.

According to the term `selfish brain`, neurons exclusively express GLUT3, which has highest glucose affinity and transport capacity. This ensures a continuous influx of glucose into neurons even if the concentration of glucose in interstitial fluid is low.

The authors should at least mention that Glut3 translocation to the plasma membrane is necessary for neuronal glucose uptake. Downregulation of Glut3 leads to hypometabolism, too. In general, inhibition of AKT-signalling seems to reduce neuronal uptake of glucose (Fehsel et al. 2022).

Although insulin is not directly involved in neuronal glucose uptake, it is noteworthy that insulin takes part in increasing glycogen content in astrocytes. Thus, insulin resistance might not directly influence glucose metabolism, but impair energy storage!

I suppose that the authors can address their model of vascular dysfunction and neuronal glucose deprivation

also for neuropathies!

The model is based on the assumption that transport of glucose and insulin to the brain is reduced.**What about insulin synthesis inside the brain?**

Although I fully agree with your model, I`m not sure, whether you sufficiently validated your model experimentally and secured it statistically.

Regarding the theoretical model, I have to admit that I can`t comprehend all calculations.

Please make your model more clear; propably by giving some examples. I don`t see the benefit for the clinical use.

Minor remarks:

Please substitute the abbreviations in the legends. It is very tedious to look up the meanings.

Lower part of Fig.1B is missing including the curve for k8'=5.5

Fig. 1c/ 4/ 5 – measuring units are missing

Please revise the references; names of journals are missing (Begg), title and year of publication (John Thomas Sorensen) are missing, duplications (Mehran), Watve (2012 and 2013 have the same title and doi)

John Thomas Sorensen should be named under `S`. John and Thomas are his first names.