Review of: "Structure of the Blood Brain Barrier and the Role of Transporters in the movement of substrates across the barriers"

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Potential competing interests: No potential competing interests to declare.

The review by Singh and Vellapandian propose an overview of the “structure of the blood brain barrier and the role of transporters in the movement of substrates across the barriers”. I quite liked the last part of the manuscript dealing with ‘barrier’ enzymes and transport systems, but I found the first part rather list-like and repetitive (do we really need to know in all detail the constitution of the different junction molecules?). I feel that there are numerous reviews on the structure of tight junctions and the cellular make-up of the blood-brain barrier and I do not think there is a need for another review on that aspect. However, reviewing the importance of ‘barrier’ enzymes and transport systems is more original and enables to emphasize the selective aspect of the blood-brain barrier. I would therefore recommend to drastically shorten the first part and develop the more original aspects of ‘barrier’ enzymes and transport systems more. In addition, several other points, detailed below also need to be addressed. Finally, I would suggest to have the manuscript read by a native English speaker, because I fell that the word choice and sentence structure sometimes complicate understanding (I do not consider it part of my job to indicate those occasions).

Points of criticism

1. Abstract: The Trojan horse mechanism is mentioned with any introduction. Please, add some words to help those readers who are not familiar with the concept.
2. Introduction: The introduction would benefit from the formulation of a central question that would help the reader to get some idea of the structure of the article.
3. Introduction, bottom of page 2: “The term blood brain barrier was first introduced by Lewandowsky and co who injected the dyes (Trypan blue, Prussian blue) through intravenous route and observed that dye had little or no effect on the CNS but had stained other organs of the body indicating that BBB prevents substances from entering the brain.[4][5]” This seems to me as a historically incorrect account. While it is true that Lewandosky and other researchers at the time had repeatedly observed the uneven organ distribution of many dyes, he did not proposer the term blood brain barrier. Instead, it seems to me that the idea and the terms of a selective barrier was proposed by Stern & Gautier, Arch. Intern. Physiol., 1921. Please, rephrase accordingly.
4. Introduction, page 3: “Although BBB acts as a protective barrier for the brain from several unwanted cells…” “The immune privilege site like the brain with its barrier restricts the immune cell entry inside the brain.[14]” These sentences contribute to maintain an old, but wrong, dogma, according to which the blood-brain barrier prevents cellular traffic. This is wrong as immune cells routinely patrol the brain perivascular spaces and tumor cells can infiltrate the brain. See

for short reviews on these points: Bechmann et al., Trends Immunol., 2007 and Galea et al., Trends Immunol., 2007. Please rephrase accordingly.

5. Introduction, page 5: “Thus, various molecules which cross the cerebral endothelial cells are thus made in contact with ecto and endo enzymes present within endothelial cells containing a high density of metabolically active organelles like mitochondria.” The authors need to introduce the notions of ecto and endo enzymes, otherwise they will lose some readers.
6. BBB structure and transport routes, page 6: The difference between the BBB and the neurovascular unit should be covered in more depth.
7. BBB structure and transport routes, page 7: “Distinct layers of endothelial cells are present in large arteries and veins, whereas a single layer of endothelial cells facing the lumen of vessel is present in the smallest capillaries of the CNS. [50]” This sentence can be interpreted to suggest that several layers of endothelial cells surround arteries and veins. Please, rephrase.
8. Figs. 3 and 4: Microglia and perivascular macrophages are presented in these figures, but are not discussed in the text. Please, add a discussion of these cells to the text of the manuscript.
9. BBB structure and transport routes, page 9: “… conceded by immune replica electron microscopy.” What does this mean? Please, clarify in the text.
10. BBB structure and transport routes, page 9: “Claudin 11 (oligodendrocyte protein) is a major component of CNS myelin.” This is irrelevant for the subject of the review and should be removed.
11. Transport pathways across the blood brain barrier, page 14: Please, provide a reference for the following statement “However, the transient inhibition of P-gp by antidepressants enables medicines such as anti-cancer drugs to enter the brain.”
12. Transport pathways across the blood brain barrier, page 14: Please, write out a. k. a..
13. Conclusion: “The Glutamine, being neurotoxic, is removed from the ECF of the brain through the most active transporters -EAAT present in astrocytes and glycine is removed by systems A and N.” This should either be removed from the conclusion or discussed in more depth in the body of the text.
14. What is the role of the additional references as compared to the references?