

Responses to the Reviewers' and Editor's Comments

Manuscript NO.: 55540

Manuscript title: " The current understanding of glucose transporter 4 expression and functional mechanisms"

The authors would like to thank the reviewers and editor for the time and efforts, especially those excellent comments. We have revised the manuscript according to the reviewer's comments.

Here are our responses to the reviewers and editor's comments line-by-line. The comments are shown first, which are followed by our responses in italics.

Please note that the words and sentences that have been revised are highlighted in yellow. In addition, we have deleted and added references. Therefore, the reference list can be considered revised.

1. **Reviewer #1:** The review is interesting but in my opinion requires some changes that I indicate below: 1) The part concerning "Carbohydrate digestion and absorption" could be eliminated. 2) All descriptions relating to the search in pubmed could be deleted. 3) All tables must be more concise because in the current form they are difficult to read. 4) In the text, instead of indicating the methods and antibodies used (already visible in the tables), it may be more appropriate to highlight the results obtained, and compare them in the "summary and perspectives

Responses: Thank you for the comments. Here are our responses.

1). We agreed with the reviewer and have deleted the "Carbohydrate digestion and absorption" section.

2). *Thank you for the suggestion, we have revised the language to only show the key words, but not the retrieved hits.*

3). *We have revised all tables so that they are more concise and easier to read.*

4) *After each table, we have added a paragraph to summary the results discussed. In so doing, the readers may get the highlights directly. Please see the revised manuscript for the changes.*

2. **Reviewer #2:** The manuscript content is adequate and attractive. A revision of the entire manuscript to edit some punctuation, grammar and typo errors is desirable. For example: Macronutrients and macronutrients... I suggest to reduce the introduction and, please, highlight the innovative content as this transporter is often revised. As in: Vargas E, Podder V, Carrillo Sepulveda MA. Physiology, Glucose Transporter Type 4 (GLUT4). In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020. Klip A, McGraw TE, James DE. Thirty sweet years of GLUT4. J Biol Chem. 2019;294(30):11369-11381.

doi:10.1074/jbc.REV119.008351 (included in your manuscript) On the conclusions section please include other attractive findings (not just involving the CNS). I suggest you to additional comments regarding the structure. If well just the crystal are for other GLUT on the PDB, some recent findings are attractive

Responses: Thank you for the comments and suggestions. Here are our responses. 1). We have revised the entire manuscript and edit the text to minimize any mistakes.

2). *We have deleted the “Carbohydrate digestion and absorption” section to reduce the introduction section.*

3). *We have cited the two references indicated by the reviewer. 4) At the end of each section (Muscle, Adipocytes, Heart and Brain sections), we have added one paragraph to summarize the findings.*

5). *We have added one paragraph to discuss the structural features and functional mechanisms of major facilitator superfamily (MFS) transporters, which glucose transporters belong to. One reference was cited. This reference is also referred on the Protein Data Bank related to GLUTs. Please see our revised manuscript for these changes.*

3. **Reviewer #3:** The authors did a general review of the literature on the problem they presented. However, I found unnecessary to pointed out the number of articles revised, instead, they must show critically the actual knowledge and future directions. It is not clear which is the interest in the methodology, if the results obtained with are not explained. Therefore, also the conclusion is not clear. Moreover the figure showing the mechanism of Glut 4 translocation is quite general. Results: the text is poor and tables indicate the same information.

Responses: Thank you for the comments and suggestions. Here are our responses.

1). *We have revised the language and deleted the number of articles retrieved. Only key words used for the search remain.*

2). *We have added one paragraph after each table to summarize the knowledge and indicate future directions.*

3). *The reason for the interest in the methodology is for readers to evaluate tools to study GLUT4 system.*

4). The figures are used to help readers to understand the current understanding of the general processes. We have revised and edited the text to minimize mistakes. All the tables are revised to become more concise and clearer. The content of each table has been explained in the text. Please see the revised manuscript for the changes.

4. **Editor's comments.** The review is interesting but reviewer requires some changes: The part concerning "Carbohydrate digestion and absorption" could be eliminated; All descriptions relating to the search in pubmed could be deleted; All tables must be more concise because in the current form they are difficult to read; Reduce the introduction and, please, highlight the innovative content.

Responses: Thank you for your comments and suggestions. Here are our responses.

1). We have deleted the "Carbohydrate digestion and absorption" section.

2). We have deleted the number of articles and significant part of the descriptions. We only retained the key words.

3). All tables have been revised to become more concise and clearer. A paragraph has been added after each table to summarize the major findings to help the readers to get the innovative content. Please see the revised manuscript for the changes.

4). We will follow other requirements as suggested for submission.

5). All issues raised have been addressed.