Dear Dr. Ying Dou
Science editor
World Journal of Hepatology

Manuscript Number: 41893 - Manuscript revision

We would like to thank the reviewers and the editorial board for the comments regarding our original manuscript entitled: *"Hepatic encephalopathy: lessons from preclinical studies."*

We believe that the recommendations were of great relevance to improve the clarity and quality of the information contained in the manuscript.

Please find below a point-by-point response to the questions and recommendations of the reviewers. All modifications are written in red characters in the revised manuscript to ease reevaluation. We have also checked and revised the manuscript according to CrossCheck report.

Sincerely,

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Answer to reviewers and action taken

Referee ID 03529813

Dear authors, first of all, congratulations for the manuscript. Although the text is well written, the discussion of each model of hepatic encephalopaty is very short and you should think to improve it before publication and also to explain better the pros and cons of each model.

Answer: We would like to thank the reviewer for the valuable comments. As requested, we expanded the discussion regarding the available models of hepatic encephalopathy. We also added in the revised manuscript a description of the carbon tetrachloride (CCL4) model as well as of models of hepatic encephalopathy induced by excessive administration of ammonia in the absence of liver failure or portocaval shunting. Importantly, the advantages and disadvantages of each type of hepatic encephalopathy model were included in the text and summarized in a new table (please see table 1 of the revised manuscript).

Also in the text it is stated that "Ideally, models of HE associated to portosystemic shunting (type B) and due to chronic liver disease (type C) must exhibit liver cirrhosis...". This paragraph may lead to misunderstandings since type B encephalopathy does not occur only in cirrhotic patients, in fact most of the case have no chronic liver disease, so may you explain why the models for type B should exhibit liver cirrhosis?

Answer: We do agree with the reviewer comments. Accordingly, the above-mentioned statement was removed from the text. In fact, we also rephrased the manuscript in order to describe the hepatic encephalopathy models classified as type B and type C in separated sections.

Referee ID 03350345

Dr Lima et al present a review article on Hepatic Encephalopathy (HE) animal models. This article give a rapid overview on the available models in the study of HE pathophysiology. Some shortcomings are however present: - it would be important for the reader to state for each model whether it is associated with hyperammonemia and systemic inflammation (cf the pathophysiology section). This should be added in the text and the tables.

Answer: This is a very pertinent comment. Accordingly, we have included in the revised manuscript a figure showing potential pathophysiological features of each model, especially hyperammonemia, inflammation, neurotransmitter changes, metabolic changes and oxidative stress (please see figure 1 of the revised manuscript).

In Introduction, the references 2 and 9 are very general and do not clearly state for what they are appealed.

Answer: We do agree with the reviewer comment. We removed the references 2 and 9 from the introduction section. Accordingly, we also removed the following statement, where the references 2 and 9 were cited "Recently, some studies have reported patients with hyperammonemia that developed minimal hepatic encephalopathy (MHE) without clinical manifestations, but with biochemical and morphological alterations in the skeletal muscle and gastrointestinal tract".

In session 3.1, it would be interesting to talk to the reader about the possible local production of ammonia in enterocytes.

Answer: This is a quite interesting comment of the reviewer. Accordingly, we have added a paragraph on this issue in the revised manuscript (2nd paragraph, page 5).

In section 3.1, just before section 3.2, mention of some work about lowering ammonia agents could be tied (Rockey et al, Hepato 2014, Weiss et al Fund Clin Pharmaco 2017, STOP-HE study by Ocera pharmaceuticals).

Answer: This is a very pertinent suggestion of the reviewer. Accordingly, we have mentioned one of the recommended studies in the last paragraph of the section 3.2.

Section 3.2, CXCLI is probably CXCL-1.

Answer: The abbreviation is corrected as requested.

The carbon tetrachloride (CCL4) model should be discussed since its has been used by some authors. What about the model of just giving hyperammonemia diet to Wistar rats ? some teams use this model

Answer: We would like to thank the reviewer for the valuable comments. As requested, we have added a description of the carbon tetrachloride (CCL4) model as well as a section to mention the hepatic encephalopathy models induced by pure hyperammonia in the absence of liver failure or portocaval shunting, including ammonia enriched diet (2nd paragraph, page 15).

Tables should be reformated : clinical signs should be separated from biological findings.

Answer: Tables were revised as requested.

A figure would be helpful.

Answer: Following the reviewer suggestion, we have included a figure showing potential pathophysiological features of each model, especially hyperammonemia, inflammation, neurotransmitter changes, metabolic changes and oxidative stress (please see figure 1).

Referee ID 00030603

Nice review about preclinical studies in hepatic encephalopathy.

Answer: We would like to thank the reviewer for his/her positive comments on our manuscript.