

ANSWERING REVIEWERS



March 15, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9358-edited.doc).

Title: Alterations of enterocyte mitochondrial respiratory function and enzyme activities following traumatic injury

Author: Ke-Jun Zhu, Hong Huang, Hui Chu, Hang Yu, Shi-Ming Zhang,

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 9358

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) The comment of Reviewer (00852498): However being of potential clinical relevance, this paper will need major revision to be more understandable and follows the usual way of writing a scientific paper. The abstract is not clear because it does not state clearly the question that the authors aim to answer. Particularly, it would be useful that the authors explain the context and the state of the art in the introduction. The first use of abbreviation should be defined. The discussion should be rewrite to follow the usual order: briefly summarize the main result, compare the result with the published data, explain the limitations of the study and finally explain why this result is interesting and could change the future clinical practice. I think that there are a few other limitations that the authors have not stated, like the limited number of rats per group, the fact that the study was done on rats and not humans,... I do not share the enthusiasm of the authors when they are writing as a conclusion that "This study defines a new strategy to attenuate gastrointestinal complications after TBI by protecting mitochondrial function of intestinal epithelial cells." Because it was not the subject of the study and the authors have not studied how to protect motichondrial function, they have just studied how the mitochondrial function was altered. So I think that they cannot conclude that.

The authors' Answer: The problem about format and form has been in accordance with the requirements; the limitations expert pointed out have been added to the dicussion; the reviwer thought the description "This study defines a new strategy to attenuate gastrointestinal complications after TBI by protecting mitochondrial function of intestinal epithelial cells." has been modified on account of the lack of appropriate.

Special thanks to the reivewer for his good comments.

(2) The comment of Reviewer (00775802): This is a very interesting paper on the study of rat enterocyte mitochondrial respiratory function and activities of related enzymes following the TBI. Their findings demonstrated that rat enterocyte mitochondrial respiratory function and activities of PDH and KGDH decline following TBI. Activities of mitochondrial complex I and II are also changed after TBI. It provided evidence for the enterocyte mitochondrial dysfunction induced by the TBI, and my concerns on the current paper are as following: 1) Abbreviations should be defined when first used in the abstract or in the text. (e.g., pyruvate dehydrogenase (PDH); α -ketoglutaric

dehydrogenase (KGDH); malate dehydrogenase (MDH)... 2) The English writing of this paper should be improved. Suggest that the manuscript be proof-read by a native language speaker to remove grammatical and typographical errors throughout. (e.g., page 9 change "reslut" to "result"...)

3) On page 9, the authors mentioned that "We hypothesis the formation of first trough may be relative to intestinal ischemia, while the second trough may be just associated with intestinal reperfusion and intracranial hypertension." as well as the last sentence on the same page "We speculate on possible scenarios that complex III and IV may correlate with chronic oxidative stress, while complex I and II just are responsible to acute mitochondrial injury" Please add related references to support the hypothesis.

4) On page 8, the authors mentioned that "So we hypothesized mitochondrial dysfunction may play an important role in TBI-induced gastrointestinal dysfunction" however, in the current study, the authors just measured the rat enterocyte mitochondrial respiratory function and activities of related enzymes following the TBI. There is no direct evidence of gastrointestinal dysfunction induced by TBI.

5) In Table 1, please clarify the meanings of abbreviations (e.g., RCR and P/O).

The authors' Answer: The first, second and fifth comments involved with writing and English express have been revised; For the third comment, we tried to combine the research of others to explain the phenomena observed in our research. Our statement were just speculation and hypothesis. According to expert opinion, we adjusted our description and added related references. For the fourth comment, although there is no direct evidence in our study to support gastrointestinal dysfunction was induced by TBI. But as we mentioned in the introduction, the fact that TBI caused gastrointestinal dysfunction has been confirmed in a number of previous studies.

Special thanks to the reviewer for his good comments.

(3) The comment of Reviewer (00220901): In the experimental study by Zhu et al. "Alterations of rat enterocyte mitochondrial respiratory function and enzyme activities following traumatic brain injury." the authors have investigated the alterations in enterocyte mitochondrial respiratory function in male rats after traumatic brain injury (TBI). The study is original and the findings are interesting. I have several comments as follows: 1. In the last paragraph of Introduction section instead of writing "... to reveal the laws of the alterations of rat enterocyte...." it would be better to write "... to reveal the mechanisms of the alterations of rat enterocyte....". 2. The results are derived only from male rats and there could be sexual dimorphism in enterocyte functions. Therefore the authors need to mention this limitation of the study in discussion section. 3. There are some literature data regarding the effects of pituitary hormones (glucocorticoids, prolactin and growth hormone) on intestinal metabolism and development. Recent clinical (Tanriverdi F. et al. Clin Endocrinol (Oxf). 2008, 68(4):573-9, Tanriverdi F et al. Brain Inj. 2007, 21(4):433-9.) and experimental (Kasturi BS, J Neurotrauma. 2009 26(8):1315-24.) data clearly demonstrated that TBI may cause acute and chronic pituitary dysfunction. This interesting detail could be discussed briefly in discussion section. 4. There are lots of abbreviations (PDH, RCR, BCA, BSA, KGDH etc...) throughout the text. Please write the open forms of them when using in the text for the first time.

The authors' Answer: Thank expert for his friendly and constructive advice. The review recommended that "... To reveal the laws of the alterations of rat enterocyte... " would be better to write "... To reveal the mechanisms of the alterations of rat enterocyte... .. ". This problem has been corrected; the limitation "The results are derived only from male rats and there could be sexual dimorphism in enterocyte functions" expert pointed out has been added to the discussion; Experts have suggested that effect of pituitary hormone on intestinal function should be joined into the discussion, And we have done so in the paper; Finally, We have wrote the open forms of abbreviations (PDH, RCR, BCA, BSA, KGDH etc...) when using in the text for the first time.

Thank expert again for carefully reading the manuscript and suggestions.

(4) The comment of Reviewer (00506034): Authors explored the alterations of rat enterocyte mitochondrial respiratory function and enzyme activities following traumatic brain injury (TBI). Mitochondrial dysfunction may play an important role in TBI-induced gastrointestinal dysfunction.

The paper is interesting and new. However, it is still some of the problems. They should also study mitochondrial morphology, ultrastructural changes and mitochondria - Related Genes following traumatic brain injury(TBI).

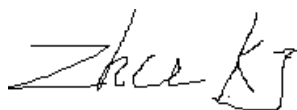
The authors' Answer: The experts put forward the comment tha the lack of mitochondrial morphology, ultrastructural changes and mitochondria Related Genes in our study, We think this is a very good suggestion, provides the direction for our further study. In fact, the TBI mitochondria microstructure changes have been reported, such as in our discussion mentioned in dicussion part: " Previous studies have revealed the occurrence of mitochondrial swelling, matrix destruction and reduced enterocyte numbers following TBI^[5,27] ". Considering the main purpose of this paper is to investigate the change of mitochondrial respiratory function., related genes not involved in discussion part, we have modified the discussion part with this consideration.

Thank expert again for carefully reading the manuscript and suggestions.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Zhu KJ', with a stylized flourish at the end.

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