Response Letter

July 12, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17821-manuscript).

Title: The pathophysiology of chronic pancreatitis induced by Dibutyltin Dichloride (DBTC) joint Ethanol in mice

Author: Zhang Hong，Liu Bin， Xu Xiao-Fan，Jiang Ting-Ting，Zhang Xiao-Qin, Shi Ying-Li, Chen Yu, Liu Fang, Gu Jie , Zhu Lin-Jia, Wu Nan.

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO.: 17821

Thanks for your response and reviewers comments on our manuscript. We sincerely apologize for the long time it has taken us to respond to these comments.

We have modified the paper according to the comments of reviewer and editor. Our detailed responses are to be found below. Our reply to the reviewers is in italic and bold.

I. Review’s comments

[Reviewer #1]

The manuscript by Zhang Hong describes the pathophysiology of chronic pancreatitis model induced by Dibutyltin Dichloride (DBTC) joint Ethanol drinking in mice The manuscript is relatively well written, data are sound, statistical evaluation is good. The model is suitable to study the mechanism of pancreatic fibrosis in chronic pancreatitis.

[Reviewer #2]

The manuscript revised: Zhang Hong et al: The pathophysiology of chronic pancreatitis model induced by Dibutyltin Dichloride (DBTC) joint Ethanol drinking in mice The authors describe a mouse model of chronic pancreatitis

induced by a single DBTC injection associated with ad libitum alcohol consumption. This model has been used to experimental studies in rats but not in mice. They reproduce progressive histological and biochemical pancreatic changes after acute pancreatitis. The methods are well described and suitable to characterize the pathological events in the pancreas. The results are well presented and the original aim is accomplished: a chronic pancreatitis model in mice is described. The model permits to investigate the progression of acute pancreatitis towards a chronic process.

Criticism:

(1) Alcohol increased the toxic effect of DBTC in rats. However, the authors postulated that the presence of gallbladder in the mice might produce some difference in the effect of DBTC. Demonstration of DBTC effect without alcohol is lacking in this work. It would be useful to add at least a group of mice on drinking water, without alcohol, receiving a single DBTC injection.

Answers: In our pre-experiment, one group of mice without alcohol, receiving a single DBTC injection has been used. The result showed that the pancreatic injury was not so serious at 1w and there was no obvious pancreatic fibrosis at 4 or 8 week. Our result suggested that alcohol could enhance the pancreatic lesion induced by DBTC. The method of DBTC joint alcohol is more suitable to induce chronic pancreatitis with pancreatic fibrosis.

(2）Chronic alcohol consumption did not induce chronic pancreatitis in mice, or in any other animal species. However, fibrosis and ultrastructural changes were described. Another group of mice only with alcohol and without DBTC injection also could be of interest and could complete the experimental design.

Answers: In our pre-experiment, another group of mice only with alcohol and without DBTC injection has also been designed. We found that there was no histological change could be seen in the group. Jing Li et al (Pancreas, 2008,37(2),189-195) found that there was little

histological change in pancreatic tissue but obvious ultrastructural changes in acinar cells of the group drinking 25% concentration of ethanol for 6 months. Their result suggested that long-term alcohol consumption did not cause chronic pancreatitis but impaired exocrine pancreatic function. In our experiment, the mice were given 10% concentration of ethanol for only 8 weeks. So it is easy to understand the reason that we could not find any histological change in pancreatic tissue.

Our result showed that long-term alcohol ingestion could not cause chronic pancreatitis, but could enhance the pancreatic lesion induced by DBTC. The method of DBTC joint alcohol is more suitable to induce chronic pancreatitis with pancreatic fibrosis.

（3） Bilirubin level was markedly increased during the experimental period. Did the authors examine liver histology? If yes, what kind of liver damage was found?

Answers: We examined liver histology and found obvious necrosis in hepatic cells 3d and 1w after demonstration of DBTC joint ethanol. At 2w, hepatic stellate cells were activated and hepatic necrosis were replaced by the liver fibrosis. At 4w and 8w, the liver fibrosis increased and many pseudolobuli formed in liver tissue. The result about the liver fibrosis induced by DBTC joint ethanol will be shown in another manuscript.

(4) English language of the manuscript requires revision, corrections.

Answers: We checked the program and spelling in English and corrected some mistakes.

II. Edit manuscript

Answers:

1) We have abbreviated the title to 12 words.

2) The sections of "Conflict-of-interest" and "Data sharing" in PDF format have been inserted to the manuscript.

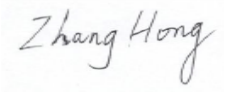
3) About Figures and Graphs . We provide separate images and

decomposable graphs in a special file.

4) 10 references were added to meet the requirements of 30 references . The lists of PMID and DOI have been edited and rearranged. We have provided the full paper which has not PMID or DOI in the Reference. (No.12 and 28)

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

Sincerely yours,



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