September 14, 2016

Ze-Mao Gong
Science Editor, Editorial Office
Baishideng Publishing Group Inc.

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 29010
Title: Effects of asymmetric dimethylarginine on renal arteries in portal hypertension and cirrhosis

Dear Ze-Mao Gong,

Attached please find the revised manuscript which I hope you will find suitable for publication in World Journal of Gastroenterology. We welcome the comments from the reviewers about the relevance of our manuscript: Reviewer #00068278: "The study is a well-designed and conducted one. It may contribute to the pathophysiology and to the development strategies to prevent/treat of hepatorenal syndrome" and Reviewer #00034635: "These results show that ADMA may induce renal arterial vasoconstriction in BDL cirrhosis but not in pre-hepatic portal hypertension animals, thereby it suggests the importance of liver dysfunction in endothelial-dependent renal vasoconstriction of cirrhosis." I have complied with the reviewers' comments and suggestions, and changes have been made accordingly. I believe that the readability of the manuscript is now improved. Below, please find the point-by-point replies to the Editor and reviewers. All revisions in the updated version of the manuscript are highlighted in yellow.

Answers to the Editor's Comments

The English language has been carefully reviewed throughout the manuscript by a native speaker of English. I believe that the readability of the manuscript has been improved.

Comment #1. The "Scientific Research Process" will be uploaded with the revised manuscript.

Comment #2. The manuscript has been revised according to the reviewers' comments and suggestions.

Comment #3. The supportive foundations section has been rewritten in order to include only the grant with a certificate of funding.

Comment #4. The “Institutional review board statement” and “Institutional animal care and use committee statement” sections have been duly completed.

The abstract has been rewritten in order to comply with the specifications of the journal:

Comment #5. The AIM section of the abstract has been rewritten and meets the word limit.

Comment #6. The METHODS section of the abstract has been rewritten and fulfills the minimum word requirement.

Comment #7. The RESULTS section of the abstract has been rewritten and fulfills the minimum word requirement.

Comment #8. The CONCLUSION section of the abstract has been rewritten and meets the word limit.

The Audio MP3 of the Core Tip for the paper will be uploaded along with the revised manuscript.

The abbreviated author names and the manuscript title are provided in the Citation section.

Comment #9. We have checked the references to eliminate repeats.

Comment #10. We have inserted the figures as PowerPoints in order to facilitate their editing.

Answers to reviewers

Reviewer 00068278

I thank the reviewer for the comments.

Sincerely,
P. Medina

Reviewer 00068215

The manuscript's English has been carefully reviewed. I believe that the readability of the manuscript is now improved.

Sincerely,
P. Medina

Reviewer 00182864

I thank the reviewer for the comment.

Sincerely,
P. Medina

Reviewer 00050424

Renal dysfunction in cirrhosis is a common complication, characterized by marked renal artery contraction as a consequence of the activation of several vasoactive pathways. NO plays a significant role in the maintenance of normal vascular tone in the renal vascular bed. Therefore, the increased inhibitory effects of ADMA on NO synthesis in renal arteries from BDL rats could be another factor contributing to the vasoconstriction associated with cirrhosis. The DDAH activators and ADMA-reducing agents may be a potential therapeutic approach to managing the vascular renal dysfunction associated with cirrhosis. On page 18, a paragraph has been included which states the possible clinical significance of the results obtained in our study.

I thank the reviewer for the comments.

Sincerely,
P. Medina

Reviewer 00034635

In a previous study, we demonstrated an increase in the plasma levels of ADMA in patients with decompensated alcoholic cirrhosis (Lluch et al., 2004, J. Hepatol 41:55-59) and in others with an acute decompensation of alcoholic liver disease (Mookerjee et al., 2007 Hepatology 45: 62-71). This increase is moderate (two-fold elevation in ADMA); however, it has been proposed that small changes in the plasma levels of ADMA may be sufficient to alter NO production by endothelial cells significantly (Wilcken et al., 2007 Mol. Genet. Metab. 91: 309-317). Cellular studies demonstrate that ADMA accumulates inside endothelial cells, reaching values 5-10 times higher than those outside the cells (Cardounel et al., 2007 J. Biol. Chem. 282:879-887). Therefore, small changes in the plasma levels of ADMA would be expected to have a large effect on the intracellular levels of this NOS inhibitor (Cardounel et al., 2007 J. Biol. Chem. 282:879-887). That notwithstanding, the intracellular levels of ADMA in endothelial cells under cirrhosis are not known.

Minor comments:

1. Bile duct ligation (BDL) has been used throughout the manuscript to refer to the murine model of cirrhosis and portal hypertension.

2. During cirrhosis, several factors may influence renal artery tone. As the reviewer noted, obstructive jaundice itself may induce renal dysfunction in humans. Recently a correlation between hyperbilirubinemia, oxidative stress and renal dysfunction has been proposed (Martínez-Cecilia, et al., Redox Biology 8: 160-164, 2016). It is noteworthy that the hyperbilirubinemia observed in the BDL model could increase oxidative stress in the kidney. It is well known that DDAH activity is inhibited by oxidative stress. Therefore, it is possible that hyperbilirubinemia increases oxidative stress and inhibits renal DDAH. This possibility is discussed on page 18, 2nd paragraph.

I thank the reviewer for the comments.

Sincerely,
P. Medina