ANSWERING REVIEWERS

October 17th, 2016.

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 29788-review.doc). All modifications are highlighted.

Title: Hepatic structural enhancement and insulin resistance amelioration due to AT1 receptor blockade

Author: Vanessa Souza-Mello

Name of Journal: *World Journal of Hepatology*

Column: Editorial

ESPS Manuscript NO: 29788

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

(1) Reviewed by **00573611** - In this editorial, the author provided a brief overview of the current knowledge regarding AT1R blockade effects on sensitivity to insulin and hepatic structural alterations as well as the intersections of AT1R blockade with PPAR activation and ACE2-ANG (1-7) – MAS receptor axis. This is an interesting editorial that is well-written. The reviewer has no further comment.

Answer: I am grateful for the comments.

(2) Reviewed by **00504952** – This mini-review paper describes the role of ARB and ACEI on hepatic remodeling and insulin resistance. The author also enhances a role of local ACE system in liver. This review paper may give great ideas for clinical study. As one of clinical physician, I have some questions.

Answer: I am grateful for the questions as they really improved the quality of the manuscript. I really hope that this editorial shed light on the new strategies and applications for angiotensin receptor blockers by clinicians.

1) ACE inhibits degradation of bradykinin. Is there any role of bradykinin?

Answer: I am grateful for this insightful comment. In fact, there is a decisive role for bradykinin on the pleiotropic effects of ACEi in the liver, muscle and adipocytes. Recently, it has been shown that the treatment with bradykinin resulted in the inhibition of hepatic gluconeogenesis, besides

enhancing the glucose uptake by myocytes and adipocytes. This ensures that the increased availability of bradykinin after ACE inhibition contributes to the reduced NAFLD and insulin resistance in animals treated with this drug class. Some discussion on this topic was added to the text (page 6).

2) The author describes prevention of fibrosis in fatty liver. What is condition of fibrosis in fatty liver? Can ARB expect degeneration of liver cirrhosis like degeneration of cardiac hypertrophy?

Answer: NAFLD is a benign condition. However, it can progress towards nocive conditions such as NASH, liver fibrosis and hepatocellular carcinoma once inflammation, insulin resistance and oxidative stress are not countered. ARBs emerge as a promising strategy as it prevents from NAFLD progression towards NASH. Also, ARBs are able to attenuate liver fibrosis by reducing hepatic expression of TGF-beta1 and favoring ACE2-ANG(1-7)- MAS receptor, which inhibits hepatic stellate cells activation. These effects attributed to ARBs are detailed on page 7 and 8.

3) Is ARB (ATIR blockade) the most potent agent? When considering multiple pathway of ACE system, it looks that ACEI is also potent agent to treat NAFLD, NASH and prevent liver fibrosis.

Answer: In fact, our aim was to describe the effects of ARBs on hepatic alterations as it is a new field of study. However, I agree with the reviewer that ACEi yields beneficial effects, mainly related to a greater availability of bradykinin. New information on this topic was added to the text (page 6).

Also, I am sending in attach the certificate of proficiency in English from University of Cambridge in my name. It attests that my level of knowledge in English language is comparable to a native speaker.

Thank you once again for the opportunity to improve my manuscript.

Sincerely yours,

Vanessa Souza-Mello, RD, PhD

Department of Anatomy and Cell Biology
State University of Rio de Janeiro
Av. 28 de Setembro 87, fundos, Vila Isabel, Rio de Janeiro/RJ
20551-030, Brazil
Fax: +55 21 28688033
E-mail: souzamello.uerj@gmail.com