

World Journal of Hepatology: Beneficial effects of losartan or telmisartan on the local hepatic renin-angiotensin system to counter obesity in an experimental model

Dear Editor,

I am glad to resubmit the above-mentioned manuscript after some amendments suggested by the reviewers. The modifications in the text were highlighted to facilitate the identification.

Furthermore, some points, which were raised by the referees, could not be inserted into the text and therefore they are listed below.

We also added the grant approval document, the audio core tip, the manuscript highlights and the original figures as requested in this resubmission.

I am looking forward to hearing from you soon.

Yours faithfully,

Vanessa de Souza-Mello, RD, PhD

(corresponding author)

Reviewer 1:

I read with great interest the manuscript entitled “Beneficial effects of losartan or telmisartan on the local hepatic renin-angiotensin system to counter obesity in an experimental model”. The manuscript is well written and adequately structured. But I have some concerns regarding the quality.

Response: We are grateful for the opportunity to improve the quality of our study and we hope that the answers provided herein fulfill your expectations.

1) The number of mice included in the study is small. McPherson S and co-authors published an article entitled “A randomised controlled trial of losartan as an anti-fibrotic agent in non-alcoholic steatohepatitis” where 45 patients were enrolled, and this number was too small to get some valid conclusion, so for experimental studies the limitation for human studies could be exceeded, in order to get valid data and conclusions. But the number of experimental subjects is not a limitation factor for publishing.

Response: We appreciate your question. In fact, when dealing with animal studies, the ethical committee advises that we use the minimum number of animals to achieve the results. We performed the experiment with five samples in each group, which is ideal for experimental design. A reason for the choice of 5 is that “if something is found to increase (or decrease) in all 5 cases, then the probability that this is due to chance is $P=(1/2)^5 < 0.05$ and the experiment could be conclusive, whereas this would not be the case with 4 or fewer animals per group” [1].

2) I am missing assessment of liver fibrosis/steatosis and the authors should or add this data or explain in detail why this data are missing. I would suggest comparing their results with results published by Alam S et al. Effect of telmisartan on histological activity and fibrosis of non-alcoholic steatohepatitis: A 1-year randomized control trial. Saudi J Gastroenterol. 2016 Jan-Feb;22(1):69-76 and Zhang QZ et al. Effects of telmisartan on improving leptin resistance and inhibiting hepatic fibrosis in rats with non-alcoholic fatty liver disease. Exp Ther Med. 2017 Sep;14(3):2689-2694.

Response: We are grateful for the opportunity to comment on this important topic. We have previously shown that the hepatic triacylglycerol levels correlate strongly with the stereological quantification of hepatic steatosis. As in our experimental design (considering the time and the diet used) we do not observe fibrosis or NASH, we used this measure to evaluate the degree of hepatic steatosis, which is validated [2]. However, we added these two important studies to the discussion in order to enrich our text.

Reviewer 2:

Dear editor Thanks for your invitation. I read the manuscript entitled “Beneficial effects of losartan or telmisartan on the local hepatic renin-angiotensin system to counter obesity in an experimental model” and tried for doing an assessment. My comments are as follow: Overall comments The manuscript is well written and I found no grammatical and spelling error. I also checked some of paragraphs with google and found no cases of plagiarism.

Response: We are grateful for the opportunity to improve the quality of our study and we hope that the answers provided herein fulfill your expectations.

Abstract: The abstract of the manuscript has a good introduction and clearly presents the aim of the study. The methods have been well explained. I wish I could see numbers and statistics in the results part instead of interpretation and explaining mechanisms which should be in conclusion section or be omitted. Additionally, I think the keyword AT1r is not suitable and should be spell out. A keyword, showing the animal model of the study, should also be added.

Response: The modifications were made in the abstract and keywords.

Main text: The introduction section explains the background of the issue and propose the aim of the study well. I’m not familiar with some parts of the methods but design, sampling, randomization, ethical issues, and statistical analysis have been well presented and explained. I have no comments on the results and discussion sections and the references are also relevant and up to dated. Final Comments: The project can be accepted for publication after minor revisions. Best wishes Reviewer

Response: Thank you for the comments and for the time spent evaluating our study.

[1] Cruz-Orive LM, Weibel ER. Recent stereological methods for cell biology: a brief survey. *Am J Physiol* 1990;258:L148-56.

[2] Catta-Preta M, Mendonca LS, Fraulob-Aquino J, Aguila MB, Mandarim-de-Lacerda CA. A critical analysis of three quantitative methods of assessment of hepatic steatosis in liver biopsies. *Virchows Arch* 2011;459:477-485.