

ANSWERING REVIEWERS



December 29, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7338-Review.doc).

Title: MK-0626, a selective DPP-4 inhibitor, attenuates hepatic steatosis in ob/ob mice

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

1 Format has been updated. The corrections are shown in red.

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

(1) Reviewer 1

Incretin analogues are being increasingly used in type II diabetic patients. One of the beneficial effects that have been detected with these molecules are related to the hepatic alterations provoked by insulin-resistance, that are steatosis and nonalcoholic steatohepatitis (NASH). There is enough evidence to support that, but there isn't sufficient knowledge about the pathophysiological mechanisms that are involved. In this manuscript the authors tried to elucidate which are the possible mechanisms implicated, conducting an experimental research in steatotic ob/ob mice, treated with MK-0626, a selective DPP-4 inhibitors. They concluded that the enhancing AMPK activity (that express increased cellular energy) results in an inhibition of hepatic lipogenic gene expression. I think that it is an elegant experimental model that has to be considered for publication. I only have minor considerations: In the introduction, there have to be substituted "Other symptoms of metabolic....." by " Other comorbidities of metabolic.....". I think is more correct. In the summary paragraph, another substitution should be " ...an effective strategy for patients with hepatic steatosis" by "an effective strategy for patients with hepatic steatosis induced by type II diabetes". In table 2, in the lean mice group, there are a very low levels of plasma insulin and HOMA-score. Do the authors can explain these results?

Thank you very much for your suggestions. We corrected the descriptions as you suggested.

The 1st paragraph in the section of "Introduction", "Other symptoms of metabolic syndrome..." was corrected to "Other comorbidities of metabolic syndrome...". In the last paragraph of the section of "Discussion", " ...an effective strategy for patients with hepatic steatosis" was corrected to "an effective strategy for patients with hepatic steatosis induced by type II diabetes". As you pointed out, plasma insulin and HOMA-score of the lean mice group were too low. We recalculated these values from raw data and found that there were miscalculations. Thank you very much for your suggestion and we sincerely apologize for that. We corrected miscalculations. Please see "Revised Table 2".

(2) Reviewer 2

In the present study Ohyama et al evaluated in vivo effects and mechanism of action of a DPP-4 inhibitor (MK-0626) on hepatic steatosis in ob/ob mice. The major finding of this experimental study was that MK-0626 attenuated liver steatosis. Interestingly authors demonstrated that this effect is not

due to a decrease in food intake and/or body weight. They suggested that possible mechanisms are the inhibition of hepatic lipogenic gene expression, the enhancement of triglyceride secretion from the liver and the increase of serum adiponectin levels. Although some other studies already demonstrated effects of DPP-4 inhibitors in the prevention of liver steatosis, in this study authors evaluated several potential underlying mechanisms. This is a very interesting study about a field of growing interest. The study design is clear and adequate for the aim. Results are very well presented and are consistent with methods. Conclusions are supported by data. Some minor changes are needed: 1. Please consider to report a recent study supporting your findings (Akaslan SB et al Metab Syndr Relat Disord. 2013 Aug;11(4):243-50) 2. The evidence of the effect on adiponectin levels has been already reported (Clin Sci (Lond). 2010 Jun 8;119(6):239-50). This study should be cited. 3. Overall, some data on this issue already exist. Thus, authors should further stress more innovative aspects of their study.

Thank you very much for your suggestions. As you suggested, our research on the previous studies were insufficient. We cited Akaslan et al.'s study in the section of "Introduction" and "Discussion". The ref. number is 12. Souza-Mello et al.'s study was also cited in the section of "Introduction" and "Discussion". The ref. number is 13. Accordingly, "Another new possible mechanism" was corrected to "Another possible mechanism" in the section of "Discussion". Besides, to stress more innovative aspects of our study, we added two sentences in the last paragraph of the section of "Discussion".

3 References and typesetting were corrected.

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

Sincerely yours,

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