February 14, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8098-review.doc).

Title: Effects of globular adiponectin on diabetic rats with nonalcoholic fatty liver disease_

Author: Hong Ma, Fan Cui, Jing-Jing Dong, Guo-Ping You, Xiang-Jiu Yang, Hua-Dong Lu, Yan-Ling Huang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8098

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

Title should be less than 12 words：I have therefore changed the title "Globular adiponectin augments insulin secretion, mediates the expression of insulin receptor and alleviates hepatic steatosis in HFD/STZ-induced diabetic rats combined with NAFLD" as "Effects of globular adiponectin on diabetic rats with nonalcoholic fatty liver disease".

Running title: Adiponectin in diabetic rats with NAFLD

All figures, tables and legends have been put at the end of the paper. The figures are made by ppt.

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

AUTHORS' REPLY TO REVIEWER'S #1 COMMENTS

(1) In the Abstract, authors report about 7 rats receiving a basic diet (control group) and other 14 rats receiving a high-fat diet which were randomized to globular adiponectin injection or saline solution. Although authors identified these 3 study groups, they presented only results about the experimental group in the abstract.

Reply: Thank you for pointing out this issue. I agree with the point raised. As keeping abstract under a word limit, I focused on putting our key results into words. In reviewed manuscript, I have added the results of three groups in abstract as follows "Compared to control group, T2DM/NAFLD group had increased levels of glucolipid and decreased levels of insulin. Plasma glucose and lipid levels were decreased in the gAd-treated group, while serum insulin levels increased. The expression of insulin receptor of T2DM/NAFLD group increased compared with NC group and gAd downregulated insulin receptor expression in the livers of T2DM/NAFLD rats. Steatosis of the liver was alleviated in the gAd-treated group compared to the T2DM/NAFLD group (NAS 1.39±0.51 vs. 1.92±0.51, $P<0.05$).

(2) Details about changes in the expression of insulin receptor protein and mRNA are very interesting, but in line with previous data. On the other hand, authors completed the evaluation with the assessment of effects on steatosis. Considering that some - but not all - of these results are already known, authors should further discuss about "what this study adds to current literature". In addition, in the discussion section, they should further discuss studies about effects of globular adiponectin on fatty acids oxidation.

Reply: I accept this suggestion and add the details about effects of globular adiponectin on fatty acids oxidation to our Discussion as follows" Studies have shown that adiponectin enhances fatty acid oxidation both in skeletal and cardiac muscle as well as in the liver, thus reducing the triglyceride content in these tissues. Yamauchi et al. found that both isoforms of the adiponectin receptor could mediate increased AMP-activated protein kinase (AMPK) phosphorylation and PPARa activity by adiponectin binding in vitro, thus activating fatty acid oxidation and glucose uptake. Therefore, gAd may protect the liver from lipid accumulation by increasing insulin secretion and mediating glucolipid metabolism."

AUTHORS' REPLY TO REVIEWER'S #2 COMMENTS

(1) There are many grammatical and syntax errors and inappropriate descriptions in the text. An English proof-reading by native is mandatory before resubmitting the manuscript.

Reply: Thank you for this valuable suggestion. I have edited the manuscript by the English language editing companies.

(2) At least two propositions are redundant and should be omitted (in the Introduction, fifth line: "NAFLD has been recognized….T2DM." and in the Discussion, fifth line: "Furthermore, NAFLD has been recognized…..T2DM.").

Reply: The proposition in the Discussion was deleted as per suggestion.

(3) An explanation about what is STZ and its role in the genesis of experimental T2DM should be reported.

Reply: I thank the Reviewer for this proper observation. I have made an explanation about STZ in MATERIALS AND METHODS as follows "Low-dose STZ has been known to induce mild impairment in insulin secretion, which is similar to what is observed in the later stages of T2DM."

(4) Some acronyms have to be explained the first time they are used (STZ, NAFLD, ISI, etc…).

Reply: Corrected as per suggestion.

(5) The way of measuring the score of staining (percentage of positive areas multiplied by the intensity of staining) is arguable: in this way the final score strongly depends from the intensity of staining (weak, moderate, strong and very strong) that is obviously very subjective…

Reply: Although the result of score of staining is subjective, in our study, the histopathological grading and staging of the NAFLD biopsies were performed by two liver pathologists using Brunt's criteria. Furthermore, in each of the three groups, the results of insulin receptor protein expression obtained by immunohistochemical staining were identical to those obtained by western blotting which is more objective.

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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