# ANSWERING REVIEWERS

May 13, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16097-review.doc).

**Title:** Female SDT fatty rats develop NASH-like hepatic lesions

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**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 16097

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

1 Format has been updated

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

**Reviewer 1:**
There are several spelling, punctuation and grammar errors in the whole text. The manuscript should be rechecked and afterwards must be resubmitted before a detailed review

**[Answer]**
Thank you for your advice. We had polished our manuscript with NPG Language Editing before resubmitting, and the certification to confirm servicing of my manuscript attached in the attachment.

**Reviewer 2:**
1.The mice show hyperglycemia, but it is caused by hypoinsulinemia as the authors stated. In human NASH, insulin resistance is an important metabolic abnormality, and the serum insulin levels are higher than those in normal controls. The authors should show the kinetics of serum insulin levels, and discuss on the point.

**[Answer]**
Thank you for your advice. The expression “hypoinsulinemia” was inappropriate. Our previous study has shown that insulin levels in SDT fatty rats increased elevated until 6 weeks of age and thereafter gradually deceased, but were significantly higher than those of SD rat until 20 weeks of age (8.89 ± 7.07 ng/mL vs 1.42 ± 0.49 ng/mL, $P < 0.05$). From 20 to 40 weeks of age, insulin levels in SDT fatty rats slightly greater than those in SD rats. From this result, insulin levels decreased along with an increase in glucose levels in female SDT fatty rats. It is suggested that SDT fatty rats exhibit insulin resistance. The progression of diabetes in female SDT fatty rats is comparable to that seen in human. We corrected and added description in the Discussion section and marked in yellow at page 16 in line 13-20.

2.Minor points, 1.Did the mice show livre tumor (preneoplastic or neoplastic)?

**[Answer]**
Thank you for your suggestion. SDT fatty rats did not exhibit liver tumer until 40 weeks of age. It is necessary to investigate whether SDT fatty rats develop hepatocarcinoma after 40 weeks of age. We added additional description in the Discussion section and marked in yellow at page 20 in line 1-3.

3.Minor points, 2.In the Discussion, the authors should make summarized comments on the similarities and differences of the model as compared with human NASH.

**[Answer]**
Thank you for your advice. We summarized the similarities and differences between those rats and human NASH. Compared to human NASH, SDT fatty rats have steatohepatitis accompanied by metabolic syndrome, including hyperglycemia, hyperinsulinemia, and obesity, which are similar features to those of human NASH. Human NASH is strongly associated with obesity, type 2 diabetes, and dyslipidemia. In contrast, there is a difference between SDT fatty rats and human NASH. Pathophysiological features of NASH with fibrosis are observed in only female SDT fatty rats and not in male SDT fatty rats. As opposed to SDT fatty rats, the prevalence of human NASH is common in men rather than women, which might be explained by sex hormones. The sentence added in the Discussion section and marked in yellow at 20 in line 4-13.

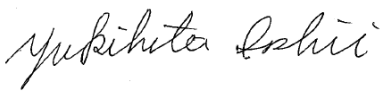
**Reviewer 3**:
The authors should explain why they use SD rats as control.

**[Answer]**
Thank you for your suggestion. We used SD rats as the control, instead of SDT rats, because we wanted to focus on the difference of pathophysiological changes of the liver between SD rats, which is normal condition, and SDT fatty rat, which is disease state. In addition, we conformed that female SDT rats only exhibit a fatty liver based on histopathology, but not fibrosis at 40 weeks of age in our previous study. On the other hand, male SDT rats, which are a severe type 2 diabetic model, does not exhibit a fatty liver and liver fibrosis at 24 weeks of age. We added those descriptions in the Discussion section and marked in yellow at page 16 in line 5-12.

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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