Reviewer's report

Title: L-Citrulline increases hepatic sensitivity to insulin by reducing the phosphorylation of serine 1101 in insulin receptor substrate-1

Version: 2 Date: 8 January 2015

Reviewer: Kenji Nagao

Reviewer's report:

This paper reports potentially valuable effects of L-citrulline ingestion to insulin sensitivity. However, I felt there are some insufficient points.

- Major Compulsory Revisions

1. In abstract, the last sentence of Result, the expression that “These results were also confirmed in animal experiments” is too rough. Specific results regarding animal experiments should be briefly described.

- Minor Essential Revisions

1. In Background, second paragraph, it is noted that “the effect of L-Cit on insulin resistance have not yet been examined.” Why did you choose L-Cit to examine? Are there any reasons or hypothesis regarding L-Cit? The reason why you choose to examine the effect of L-Cit to insulin action should be briefly explained.

2. In Result, page 11 last paragraph, Figs. 3A, B C, and D are wrong. It seems these are Figs 4A, B C, and D.

3. In Result or Materials and Methods section, SHRSP.Z-Leprfa/IzmDmcr rats should be explained. Is it obese model? Type 2 diabetes model? Please briefly explain or add a reference.

4. In Table 1, description of statistical analyses is missing. Is it significantly different in glucose level between these two groups?

5. In Figure 4, labeling “A, B, C, or D” are missing.

- Discretionary Revisions

1. To what extent feeding L-Cit elevates the concentration of Cit in liver or in plasma compared with control rats? Is it the same level as H4IIE cells were treated with 250 µM of L-Cit?

2. Have you ever examined dose-responses in L-Cit concentration? Only Figure 1 indicates two different concentrations. How did you decide the amount of L-Cit to administer to rats?

3. In vitro experiment and animal experiment, control groups are not treated with any amino acids. Have you ever examined other amino acids? Are these effects
specific to L-Cit? or other amino acids have the similar effect?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

The reviewer, Kenji Nagao is an employee of Ajinomoto Co., Inc.