Author's response to reviews

Title: Study on administration of 1,5-anhydro-D-fructose in C57BL/6J mice challenged with high-fat diet

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Version: 2 Date: 6 September 2010

Author's response to reviews: see over
Here below are our responses (in colour) to the two reviewers’ suggestions in revising our ms of “Role of 1,5-anhydro-D-fructose in C57BL/6J mice challenged with high-fat diet”

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Briefly, we have accepted all the good suggestions and related improvements have been made in the revised version submitted here.

Please do not hesitate to contact us for any further questions.

Bst rgs

Dr Bo Ahrén and Dr Shukun Yu.

1st Reviewer's report
Title: Role of 1,5-anhydro-D-fructose in C57BL/6J mice challenged with high-fat diet
Version: 1 Date: 8 June 2010
Reviewer: Sof Andrikopoulos

Reviewer's report:
Obesity and high fat diets impair glucose tolerance and contribute to disease states such as Type 2 diabetes. Interventions that can promote better glucose tolerance are therefore desirable to prevent progression to diabetes. Previous studies have shown that AF can act in an anti-oxidant manner and can improve glucose tolerance and insulin secretion in chow-fed mice. In this study the authors have used a naturally occurring sugar called 1,5-Anhydro-D-fructose (AF) to treat mice fed a high fat diet and assessed body weight gain, glucose tolerance and insulin secretion. The results showed that feeding mice AF did not affect body weight gain, glucose intolerance caused by high fat feeding or rates of insulin secretion. The authors suggest that the lack of AF may be the result of the route of administration (via drinking water) and/or that the dose may be have be lower than required. This is a well-written and presented study that shows a lack of effect in this high fat fed mouse model. I have the following comments to make:

Compulsory Revisions
1. It has been suggested that high fat does not cause oxidative stress (Moore et al. Diabetes 53, 2610–2616, 2004). It is therefore possible that if AF is acting as an antioxidant that it would not improve glucose tolerance under these conditions. This point could be further discussed.
This valuable point has been now discussed briefly with suitable citations.
2. In a previous study these authors have shown that the improvement in glucose tolerance and insulin secretion following AF treatment was associated with an increase in GLP-1 levels. It is likely that with high fat feeding the potentiating
Effect of AF to induce GLP-1 is blunted. This point should also be discussed. 
**This valuable point has been now discussed briefly with suitable citations.**

3. The plasma insulin levels shown in Fig 2A and Fig 2B should be presented on the same scale to highlight the blunting effect of a high fat diet on insulin release. 
**This valuable point has been now accepted and improved Fig. 2 is now made in the revised version.**

**Level of interest:** An article of importance in its field  
**Quality of written English:** Acceptable  
**Statistical review:** No, the manuscript does not need to be seen by a statistician.  
**Declaration of competing interests:** I declare that I have no competing interests.

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2nd Reviewer's report

**Title:** Role of 1,5-anhydro-D-fructose in C57BL/6J mice challenged with high-fat diet  
**Version:** 1  
**Date:** 30 July 2010  
**Reviewer:** Nieves Gonzalez  

**Reviewer's report:**

Mayor Compulsory Revisions  
By the present work, the authors meat to test the long-term effect of AF on insulin secretion and glucose tolerance, and also the possible responsibility of GLP-1 on the processes. For that, they used an obesity model generated in mice by a high-fat feeding. Although the methods are well described, the authors claimed that their negative results are possibly due to the low dose of AF administered; if they think so, why higher doses of the AF were not tested? 
To test a dose higher than 1.5g/kg/day used in the current study has no meaning either for AF as a drug or a health food additive. This has now been briefly discussed. 

The protocol used does not meet the porpoise rise by the authors at the end of the Introduction section; why they did not measure plasma GLP-1 levels?. No justification for performing the study in an obesity model is provided in the Introduction section. 
We were more interested in the final results, *i.e.*, if AF has or has not a beneficial effect mouse model liable for obesity development. 

We have now added additional contents and references for the justification of the current study in the “Background” section. 

The Discussion is very poor (*i.e.* 3 out of 4 references are related with the already known fact that high-fat diet induces metabolic alterations in C57BL/6J mice). The conclusions are based on a hypothesis not demonstrated by the data. 
In general terms, the data does not provide further relevant information to be added to that already reported by part of the authors in a previous publication (Ahrén B, Holst JJ, Yu S: Eur J Pharmacol 2000, 397:219-225). 

The Discussion section has been revised quite considerably with new references to meet these suggestions.  

Minor Essential Revisions  
• Statistics on insulin data (Table 1) should be revised (Normal diet value of 129±26 versus High-fat diet 211±22, n=12, p<0.05, by Student t test, RSigma).
Accepted and change has been made now.
• Statistics section, Table 1 and Figures Legends: it is confusing the way results are been expressed (mean±SEM or mean±SE?)
  It should be mean±SE and change has been made now.
• Discussion Section, lines 9 and 12: reference 11 should be 10 (Ahrén B, Holst JJ, Yu S: Eur J Pharmacol 2000, 397:219-225), which is their previous study.
  change has been made now.
Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
'I declare that I have no competing interests' below

To submit your revised manuscript
We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns. As you will see from the reports, the reviewers have provided very different advice with regard to the suitability of the manuscript for publication. Please note that given the disagreement in the reviewers? recommendations, we may need to seek further advice on your manuscript when we receive the revised version.

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Please don't hesitate to contact me if you have any problems or questions regarding your manuscript.

With best wishes,

Nina Titmus

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