Reviewer’s report

Title: Brown adipose tissue activity is modulated in olanzapine-treated young rats by simvastatin

Version: 0 Date: 11 Mar 2020

Reviewer's report:

Aim: investigate whether chronic co-treatment of statins could have lipid-lowering effects though intervening in BAT thermogenesis.

The results cannot be published without additional experiments as the interpretation cannot be valid without controlling for effects in the liver.

In my opinion, therefore, the interpretation of results is flawed. Authors fail to mention or examine at any point whether simvastatin excerts its effect via its recognized lipid-lowering mechanism of action (HMGCR inhibition in the liver). Too little emphasis on potentially low translational value (presence of brown adipose tissue in humans). Failure to provide a rationale for examining brown adipose tissue only, not liver. Important work both within clinical areas and with regard to previous works in animal models is not cited. For instance, no references are cited in the first sentence in the introduction or the discussion. Discrepancies between results presented in text and results shown in figures. In the introduction, PKA is not introduced, it appears suddenly later in the manuscript.

While the experiment itself is well designed and provided some interesting findings, I was surprised by some of the drawbacks and that they have not been addressed at all after being pointed out previously. The discussion is the major problem, in my view. In particular, the failure to mention or examine at any point whether simvastatin excerts its effect via its recognized lipid-lowering mechanism of action (HMGCR inhibition in the liver), ESPECIALLY AS A WELL-KNOWN EFFECT OF OLANZAPINE IS STIMULATION OF HMGCR IN THE LIVER. Without examining or even mentioning this issue, it seems all the more strange to go straight to the brown adipose tissue. Reduced thermogenesis is a well-known effect of olanzapine in the rat (although very few works demonstrating this are cited). If the authors believe that a reversal of this is responsible for the lipid-lowering effects of statin in this model, then the assumed mechanisms should at least be detailed in the discussion.

Introduction: hard to follow, lacks direction.

Methods: The age of the rats is not stated, although from their weight it is apparent that they were very young.

Were rats fasted prior to blood sampling/tissue harvest? This can have a major impact on results.

Results. 3.2. Body temperature: Fig 2B (not just Fig 2 as referred to): y axis should be (absolute) body temperature, not change in body temperature.
3.7. "However, there were (SHOULD READ WAS) a significant increase in PPARg expression in the O+S".... should read O group? Text not in accordance with figure.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?
5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal