Reviewer’s report

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

Version: 0 Date: 20 Jan 2020

Reviewer: David Wright

Reviewer's report:

Liu et al. examined the impact of co-treatment with simvastatin on olanzapine-induced metabolic disturbances in young female rats. They present data demonstrating that simvastatin reduces weight gain and white adipose tissue accretion and this was associated with increases in indices of brown adipose thermogenesis such as UCP1 protein content and markers of PKA signaling. While the study is novel and timely, the translatability of the reported findings clinically is limited due to the housing conditions that were used. Animals were housed below their thermal neutral zone. This places animals under a degree of stress which can dramatically alter the response to any number of perturbations. For example, McKie et al. (PMID: 31297830) recently demonstrated that catecholamine levels were ~ 2-fold higher in mice housed at room temperature compared to thermal neutral conditions. The lower levels of catecholamines under thermal neutral housing were associated with a marked reduction in indices of browning. Given these points, at the very least the authors must acknowledge housing temperature as a major shortcoming of the current manuscript. Other points that need to be addressed are as follows:

1. Starting weights of rats are given. Please provide the age as well.
2. What was the purpose of the open field test? Information regarding this for the naive reader would be warranted.
3. For the Western blot analysis, was an internal loading control used for each gel that was run? This information needs to be given. Related to this point, please provide the approximate molecular weights of the observed bands on both the representative Western blots and full gel images provided in the supplementary figures.
4. It is interesting that the authors found that olanzapine treatment reduced body temperature, which would be indicative of a decrease in energy expenditure. This is in contrast to a study by Lord et al. (PMID: 28805659) who found that olanzapine increased energy expenditure when fed to mice compounded in a high fat diet. These discrepant findings need to be discussed.
5. The authors have dosed olanzapine orally. Do the authors have any information regarding circulating olanzapine levels? Similarly, could simvastatin treatment be altering the clearance/degradation of olanzapine? These points need to be considered and at the very least need to be discussed. Ideally, this should be measured if possible.
6. The authors make the case that the beneficial effects of simvastatin appear to be mediated through the activation of brown adipose tissue. As catecholamines are primary neuroendocrine activators of brown adipose tissue activity, circulating concentrations of epinephrine/norepinephrine should be measured.
7. The last paragraph of the discussion highlights sex differences in the response to SGAs. While chronic effects of SGAs are discussed it would be worth highlighting recent findings from
Medak et al. (PMID:31499390) who found that female mice were completely protected against acute olanzapine-induced hyperglycemia

**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.

Yes

**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:

Acceptable

**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