Reviewer's report

Title: Cardiovascular autonomic dysfunction and oxidative stress induced by fructose overload in an experimental model of hypertension and menopause

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Reviewer: William H Miller

Reviewer's report:

Many thanks for the opportunity to review this work. I feel it adds to the field and promotes consideration of the interaction between menopause and other environmental factors such as diet.

The abstract and title are appropriate.

Background:
In the background the authors give a fair summary of the preceding literature.

1 - I think the authors should reference a specific set of guidelines or definitions regarding metabolic syndrome (eg the NCEP ATP III ).
(Discretionary)

Research Question:
The paper by Conti et al. seeks to address whether the previously documented deleterious effects of high fructose feeding exacerbate the negative effects seen in a rat model of cardiovascular disease and menopause. The authors chose to focus on blood pressure, autonomic regulation and markers of inflammation and oxidative stress. As such, the research question was well defined.

Methods:
In general the methods were appropriate and well described. However I have some specific questions which they may feel are worth addressing:

2 - How was the dose of 100g/L of fructose in drinking water arrived at? How does this compare to other studies?
(Discretionary)

3 - The authors state that intake of chow and water were measured – were there any significant differences, I couldn’t see this reported in the results section?
(Minor, essential)

4 - Please adjust the order of methods to make it clear how the heart tissue is removed. This is assayed in the section “Inflammatory markers on cardiac tissue”, but the description doesn’t appear until the following section.
5 - Are four hour and two hour fasting periods long enough prior to measurement of trigs and glucose, and ITT, respectively? Many other authors use overnight fasting. Please justify this time point (eg reference other appropriate articles with these shorter time points in the text).

6 - Why do the authors only utilise a direct, acute measurement of haemodynamics? This may invoke some level of stress response and given that part of their argument is for differential activation of the autonomic nervous system this leaves the effects on blood pressure etc open to debate. Have the authors considered a longer-term measurement of haemodynamics via – for example – radiotelemetric probes? Please justify the choice of acute measurement and either explain how this is unlikely to have affected the results / or acknowledge this as a limitation?

7 - Study design – I would respectfully argue that the study requires a further group, that of non-OVX rats which have received fructose in their drinking water. I view this as a major gap in the study design as it is difficult to ascertain whether effects seen in OVX / Fructose animals may have been seen in intact / fructose animals – ie that the loss of female hormones was not the crucial factor per se. Furthermore, given that the literature identifies protective roles for female hormones and negative effects of fructose diets, it may have been interesting for the authors to attempt to dissect whether the combination of OVX and high fructose are additive or synergistic. Please either provide data from a non-OVX / fructose group, or justify why this is unnecessary.

Results:
Generally ok.

8 - Can authors please clarify the situation with regard to catalase. Are they measuring concentration or activity? There seems to be some discrepancies in what they refer to between the results and discussion sections.

Discussion:
Notwithstanding my reservations about the missing animal group and the acute haemodynamics measurements, the discussion reflects the results obtained.

9 - The limitations – use of the fructose-fed SHR as a model of metabolic syndrome, the acute measurements – are not fully articulated by the authors. Please consider specifically articulating the limitations of the study
Previous work is clearly and accurately referenced.

10 - There are quite a few minor typographical / spelling / grammatical errors. Please correct these (minor, essential).

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

**Quality of written English:** Needs some language corrections before being published

**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.