Reviewer's report

Title: Metformin restores electrophysiology of small conductance calcium-activated potassium channels in the atrium of GK diabetic rats

Version: 0 Date: 13 Jan 2018

Reviewer: Umberto Barbero

Reviewer's report:

Fu et al performed an interesting study on the potential the underlying mechanism of the anti-arrhythmic effect of metformin in diabetic patients, through exploring the mechanism underlying the anti-arrhythmic effect of metformin in a T2DM rat model with a special focus on the SK channels. They studied 12 Goto-Kakizaki rats, giving them metformin for three months. After the rats were euthanized, the atrium were excised to assess the proportion of fibrotic areas and to assess the expression levels of SK channels in the atrium, western blotting was conducted. Histological results demonstrated a protective effect of metformin on the structure and electrophysiology of the atrium while Western blot results showed that the level of KCa2.2 in GK atrium was approximately half of that in control atrium and the level of KCa2.3 in GK atrium was 1.98 ± 0.5 fold of that in control atrium. mRNA real time PCR results indicated that the expression pattern of the SK channels in rat atrial myocytes was altered under diabetic conditions and metformin abolished diabetes-induced changes in the expression of atrial SK channels. English is acceptable, method well explained and statistics are correct. Conclusions are clear. Despite the small number of rat involved, it is a nice study, exploring a poorly-known field: it may be interesting for those with closely related research interests . On the whole I think the paper is suitable for publication after some minor changes:

- The number of rat studied should be added in the abstract section

- Given the small sample size, parametric distribution should be checked for

- The authors should explain in the methods why they choose a high dose of metformin (instead of a lower dose of 100mg/kg/day)

- In the introduction ,page 3 line 56 the authors say that diabetes "also confers an approximately twofold-increased risk of cardiovascular diseases" and cite an interesting but qualitative review. Since the relevance for this paper, may be more complete to cite also a quantitative analysis on the topic (see for example "Assessing Risk in Patients with Stable Coronary Disease: When Should We Intensify Care and Follow-Up? Results from a Meta-Analysis of Observational Studies of the COURAGE and FAME Era. Scientifica
(Cairo). 2016;2016:3769152” which reports indeed an OR of 1.93 for diabetes). That would add clinical relevance to the author's paper, especially because reporting the role of CRP as a cardiovascular risk factor, and metformin has demonstrated in experimental model to be able to diminish the level of CRP (Liu et al. Lipids Health Dis. 2014 Jul 15;13:115)

- I suggest to change the way the amount of metformin is reported (300 mg·kg-1·d−1) in a clearer way (for example 300 mg/kg/day)

- The footnote of figure 2 should be extended to better explain differences between ECG.

- Page 5, line 94, the author use "Met": please add it in bracket before in the text to make clear is a short form of metformin. The same should be added in the abbreviation list.

- In the methods section the numbers of rat used as controls should be written.

- In Figure 1, colore coding of staining should be added in the footnotes.

- In Figure 5 the section C is not clearly districts: it may be useful to move the capital letter "C" above

**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