Response to Reviewer 4 Comments

IJMS-3062717

TITLE: **Hypoxic cardioprotection by new antihypertensive compounds in high salt-diet hypertensive rats: Glucose transport participation and its possible pathway.**

1. Summary

Thank you very much for taking the time to review our manuscript. Please find the detailed responses below and the revisions/corrections highlighted in red/in track changes in the re-submitted files.

2. Questions for General Evaluation	**Reviewer's Evaluation**	**Response and Revisions**
Does the introduction provide sufficient background and include all relevant references?	Can be improved	*Answered below*
Are all the cited references relevant to the research?	Yes	*Thanks for your comment*
Is the research design appropriate?	Yes	*Thanks for your comment*
Are the methods adequately described?	Yes	*No comments*
Are the results clearly presented?	Can be improved	*Answered below*
Are the conclusions supported by the results?	Can be improved	*Answered below*

3. Point-by-point response to Comments and Suggestions for Authors

Comments 1: Making no reference to the proarrhythmic aspects or possibilities of your findings. In your manuscript these concepts and references are dated and are likely misleading.

Response 1: *Regarding the possibility of arrhythmias occurring, no ECGs were performed on the animals. Furthermore, no irregularities were evident during the treatments. We had no reason to suspect that arrhythmias could occur.*

Comments 2: The main conceptual updates that you are missing can be obtained from the two publications cited below and others.

- Constitutively active adenosine monophosphate-activated protein kinase regulates voltage-gated sodium channels in ventricular myocytes.

Light PE, Wallace CH, Dyck JR. Circulation. 2003 Apr 22;107(15):1962-5. doi: 10.1161/01.CIR.0000069269.60167.02. Epub 2003 Apr 7. PMID: 12682004

- Cardiac mechanisms of the beneficial effects of SGLT2 inhibitors in heart failure: Evidence for potential off-target effects.
  Dyck JRB, Sossalla S, Hamdani N, Coronel R, Weber NC, Light PE, Zuurbier CJ. J Mol Cell Cardiol. 2022 Jun;167:17-31. doi: 10.1016/j.yjmcc.2022.03.005. Epub 2022 Mar 22. PMID: 35331696

Response 2: *The first suggested article discusses the possibility that AMPK produces arrhythmias, given that it acts on sodium channels. However, it also mentions that mutations of the α-catalytic subunit of AMPK produce it. Our study observed that the compounds bind to the regulatory γ-subunit of AMPK, so we believe it is unrelated to our work.*

Regarding the other article, SGLT-specific blockers reduce glucose levels in people with diabetes. They have diuretic action that lowers the fluid volume overload in heart failure. Specifically, SGLT1 is overexpressed by hypoxia, and its inhibition can improve cardiac conditions. Its activation in ischemia activates AMPK in cardiomyocytes, and the increased activity of the SGLT1, which determines an influx of glucose, could be interpreted as a compensatory mechanism intended to improve the intracellular availability of energetic substrates in conditions of decreased oxygen supply.
This information does not explain how our new compounds could act, and we can´t relate the compounds to the inhibition of these transporters.

However, this other article is of great relevance and coincides with the obtained results. And is mentioned on line 297.

- *Bairwa S.C.; Parajuli, N.; Dyck, J. R.B. The role of AMPK in cardiomyocyte health and survival. Biochimica et Biophysica Acta. 2016, 1862, 2199–2210. doi:10.1016/j.bbadis.2016.07.001*

Comments 3: The main weakness in your paper is the Discussion section. After reading and, in fact, rereading this section, I am at a loss to be sure of your main findings or their relationship to directly relevant previous work. I recommend a complete rewrite of this section along with additions of subtitles such as:
a) Summary of Major Findings
b) Relationship to Previous Results
c) New Mechanistic Insights
d) Possible Translational Applications

Response 3: *We rearranged all the discussion using your significant recommendations. Thank you.*

Comments 4: Your manuscript is well organized and the Figures are quite clear. However, in a number of key places you use very unconventional Scientific English and this leads to ambiguities. Examples include:
- line 45 'so'
- line 55 'a crucial protagonist'
- line 71 'high contraction'
- line 72 'better patient evolution'
- line 102 'to keep ATP levels'

Response 4: *Changes have been made.*
- line 51 ′ Therefore ′
~~- line 55 ´deleted´~~
- line 76 ´excessive muscle contraction´
- line 78 ´heart survival´
- line 105 ´to maintain intracellular ATP concentrations´

4. Response to Comments on the Quality of English Language

Point 1: Minor editing of the English language is required.
Response 1: *Regarding this suggestion, we revised the whole manuscript again and analyzed it using two paid grammar and style software programs, and no errors were marked. We also asked an English speaker to review it, which helped raise the quality. We hope that these strategies have achieved the language objectives.*

5. Additional clarifications
We welcome the suggestions made by the reviewer and made all our efforts to improve our results.