OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-20-00438
Title: The iNOS-inhibitor 1400W as a potential treatment for retinal diseases
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COMMENTS TO AUTHORS

In this review, the authors have summarized the mechanisms underlying the hypoxia and oxidative stress induced neuronal death. They introduced their work using the H2O2 or CoCl2 to induce oxidative stress in porcine retinal cells culture, followed by the treatment of these cultures with iNOS inhibitor, in order to down-regulate the NO to improve the RGCs survival. The results presented in this preview are promising for treatments aiming at the rescue of RGCs in various eye diseases such as glaucoma. The original studies done by authors were well carried out, and the description of the procedures was well written.

Comments:

(1) The flow of the writing can be improved. The introduction cited the hypoxia and oxidative stress such as two independent mechanisms, while among the most common degenerative disease they occur together, having hypoxia leading to cellular stress, followed by mitochondrial stress, leading to cell damage. In the discussion, the authors also mentioned combining both hypoxic and oxidative stress in the future. Could expand this a bit (i.e. How?).

They also introduced two very different eye diseases, glaucoma and AMD. As the two eye diseases kill very different types of retinal neurons/cells, the common pathway underlying the very different diseases need to be clarified. Furthermore, the CoCl2 induced RGC death in culture could be a good model for studying RGC death in glaucoma, but the link to AMD is weak.

(2) please state what the iNOS inhibitor 1400W does in a normal tissue. Does the same dosage of 1400W induce any side-effects?

(3) It would be useful to present studies inducing hypoxia in the cell cultures plates. This model is based in a pathological process that is well studied in cancer cells, where high rates of cell proliferation lead to hypoxia and prevent the hydroxylation of proline by a-ketoglutarate. Moreover, heat shock proteins interact with HIF-1 and activates it. So, it increases the transcription of gene for proteins such as VEGF, NOS and COX-2. It is not clear why proteins, which can help in a hypoxic environment, increased the neuronal death? Thus, it is important to clarify why they used this model, to tie the pathologies together and relate that immunomodulatory peptides stimulate HIF-1 dependent gene expression even in normoxic cells (reference number 7).

(4) There are minor typos which needs to be fixed, for example, in line 36, "The iNOS-catalyzed reaction of L-arginine to Lcitrulline and NO is inhibited" is missing a clarification comma after "NO."