PEER-REVIEW REPORT

Name of journal: Neural Regeneration Research
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Title: Targeting the mitochondria permeability transition pore in traumatic central nervous system injury
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Reviewer's country: Germany
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COMMENTS TO AUTHORS

General: The authors provide a short overview on the treatment approach of preventing mPT after TBI or SCI. They focus on the pharmacological therapeutic option of applying CsA or NIM811.

For this Perspective article certainly the translational approach is of importance and therefore definitely the clinical trial performed in this area should be mentioned or included in table 1.

For example:

Mazzeo AT, Brophy GM, Gilman CB, Alves OL, Robles JR, Hayes RL, Povlishock JT, Bullock MR. Safety and tolerability of cyclosporin a in severe traumatic brain injury patients: results from a prospective randomized trial. J Neurotrauma. 2009 Dec;26(12):2195-206. doi: 10.1089/neu.2009.1012 .

Mazzeo AT, Beat A, Singh A, Bullock MR. The role of mitochondrial transition pore, and its modulation, in traumatic brain injury and delayed neurodegeneration after TBI. Exp Neurol. 2009 Aug;218(2):363-70. doi: 10.1016/j.expneurol.2009.05.026

Gajavelli S, Sinha VK, Mazzeo AT, Spurlock MS, Lee SW, Ahmed AI, Yokobori S, Bullock RM. Evidence to support mitochondrial neuroprotection, in severe traumatic brain injury. J Bioenerg Biomembr. 2015 Apr;47(1-2):133-48. doi: 10.1007/s10863-014-9589-1 . Epub 2014 Oct 31.

As in chapter "Future Considerations" also the question regarding other mPTP targeting compounds is raised, the authors may mention that there are actually a few, e.g. Erythropoietin.

(Erythropoietin and Its Derivates Modulate Mitochondrial Dysfunction after Diffuse Traumatic Brain Injury. Millet A et al., 2016, J Neurotrauma 33: 1625-33)

Details:

Introduction

Short sentence/few examples on what is meant with "up-stream cell death signaling pathways"?

The Mitochondria Permeability Transition

"However, following SCI or TBI, mitochondria rapidly become dysfunctional resulting in a

loss of cytosolic Ca2+ buffering capacity due to influx of massive pathophysiological levels of Ca2+ through glutamate receptor subtypes, the endoplasmic reticulum, free radical…, ….
Comment: Not really clear from this sentence how endoplasmatic reticulum is related to mitochondrial dysfunction.

Inhibiting mPTP Formation in TBI and SCI
"As stated above, there is strong evidence that targeting the mPTP mitochondria has therapeutic potential in the treatment…."
Comment: The word "mitochondria" seems out of place in this sentence - can be deleted? Maybe to treat the mitochondrial dysfunction has therapeutic potential? The mitochondria itself is not a therapeutic

Inhibiting mPTP Formation in TBI and SCI
"What is clear from this analysis is that the majority of labs found CsA or
NIM811 to be effective in the treatment of various TBI-related outcomes across a range of doses routes of administration and injury models."
Comment: As in general negative results are not published - as the authors mention themselves in "Future Considerations - the authors actually don't know if it is the "majority" of labs that found CsA or NIM811 to be effective. It would be possible to say "…. Many labs found…."

Inhibiting mPTP Formation in TBI and SCI
"…..NIM811 was reported to be effective in all TBI studies…."
Comment: This sentence is misleading as there seem to be only one NIM811 study in table 1

Minor
Future Considerations: "For example, the benefit of CsA administration seems to follow and inverted U-shape highlighting the need…."
Probably: "…….seems to follow an inverted U-shape…."

Table 1: Information about the study "Gabbita et al., 2005" do not reveal whether CsA or NIM811 was applied.