OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-20-00053
Title: Abnormal Glu-mGluR2/3-PI3K pathway leading to diabetes-related depression in hippocampal neurovascular unit
Reviewer's Name: Christopher J Andrews
Reviewer's country: Australia
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COMMENTS TO AUTHORS

My interest in this paper comes from a parallel contention of the role of glutamate in electrical injury hippocampal related neuropsychological symptoms, which includes depression. I was interested to learn if this paper addressed the origin of excess glutamate and the way in which it produced DD. What the paper does show is that glutamate and cortisol are involved in apoptosis in the hippocampus, and that the effect of each potentiates the other. This is useful knowledge, though it doesn't answer my desire to know the origin of the glutamate in DD. I do not criticise the paper for this, as it may be beyond their elected scope, though I am still interested in knowing the origin of the glutamate.

Nonetheless cortisol and glutamate or both neurotoxic in their own right, and the paper might be able to give an idea of which comes first to lead to the potentiation one of the other in DD. That is, the roles of glutamate and cortisol might be able to be separated.

The experimentation in the paper seems sound, and the findings useful. It answers the question of how apoptosis occurs in DD, rather than where the stimulation for the apoptosis arises. Thus there are further steps beyond, or even preceding, this paper before we fully understand DD or other glutamine effects on the hippocampus.

One technical matter is that many results are presented "compared with control". There is however no indication of how the control group was designed, how it was prepared, and what its nature was.

Incidentally, there is not an immediate indication why the barrier function required cortisol in the model. The functions of glutamate and cortisol are not well separated in the whole paper, apart from to show they potentiate each other, e.g. "the abnormal expression of glutamate receptor mGluR2/3 was closely related to the activation of glucocorticoid receptor following by imbalance of glutamate transporters expression". The role of each and any separation of their function is not considered, nor their interdependence.