OPEN PEER REVIEW REPORT 1

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Title: Cytoprotective effect of ferrostatin-1 on glutamate induced cytotoxicity in HT-22 cells through inhibiting oxidative toxicity
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COMMENTS TO AUTHORS

Strengths: the topic is timely; weaknesses: the logic and evidence of the research results are not quite complete.

This is a research article deals with protective effects of ferrostatin-1 on glutamate-induced cytotoxicity in mouse hippocampal HT-22 cells. They demonstrated that the pretreatment of ferrostatin-1 restores mitochondria function and decreases intracellular MDA levels. In addition, ferrostatin-1 also repressed ROS accumulation by upregulation of SOD, Nrf2 and GSH-Gpx. They concluded ferrostatin-1 may play a neuroprotective role in against cytotoxicity induced by glutamate. This is a well-conducted article containing interesting results which merit publication. However, the level of writing in English needs to be strengthened. I strongly recommend that this article must be revised by a native English-speaking editor. In addition, some of my questions are listed below:

1. According to previous publication, at relatively early time points (8-12 h), glutamate induced mostly necrosis, whereas at late time points (16-24 h), it induced mainly apoptosis (Eur J Pharmacol. 2009;617:1-11). It is known necrosis and apoptosis are very distinct morphologically. However, the time point chosen by the author is at the cut-off point (16 h). This makes it difficult to assess the basic pattern of cell death (for example, the Fig. 2A, the information it displays is actually very unclear). As a result, I suggest Authors should strengthen the analysis of some apoptosis or necrosis markers to enhance their evidence.
2. Similarly, mGluR5-dependent cell death signaling pathways is well established as a frequent player in glutamate-dependent cell death (excitotoxicity). I was very surprised that authors did not perform any relevant experimental evidence at all, and even the text narrative was lacking.
3. According to authors' results, ferroptosis may indeed be involved in the neuroprotection of ferrostatin-1. Although authors showed the results of GSH-Gpx and Nrf2, inactive mitochondria are usually not considered to cause ferroptosis (Mol. Cell 2019;73:354-363). Authors are better able to present more evidence of mitochondrial dysfunction such as calcium levels by glutamate-induced neurotoxicity.