Targeting ferroptosis in Alzheimer's disease: investigating glutamate-induced oxidative stress in HT-22 hippocampal neurons

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Neurobiology of Aging Research

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This study examines how a specific type of cell damage may contribute to Alzheimer's disease, which causes memory loss and cognitive decline. In addition to known protein buildup, growing evidence suggests that oxidative stress and a form of cell death called ferroptosis play key roles. Ferroptosis occurs when harmful molecules accumulate and overwhelm the cell's natural defenses, making brain cells especially vulnerable. Using mouse-derived brain cells, we simulated this damage by exposing them to glutamate and measured cell survival, gene responses, and damage levels. These findings help improve understanding of brain cell degeneration and may guide future treatments to protect against Alzheimer's disease.

Introduction

- Alzheimer's disease causes memory loss and brain cell damage, and while protein buildup is well known, other harmful processes may also contribute.
- Oxidative stress (an accumulation of harmful molecules overwhelming the body's defense mechanisms) can damage brain cells and trigger ferroptosis, a type of cell death linked to iron imbalance.
- Ferroptosis occurs when the cell's protective system fails, leading to toxic buildup that damages cell membranes.
- Brain cells are especially vulnerable to this damage due to their high energy needs and limited ability to handle stress.
- This study uses mouse-derived brain cells (HT-22) to model this process and better understand how oxidative stress leads to cell death, with the goal of identifying new ways to protect the brain from neurodegeneration.

Methods

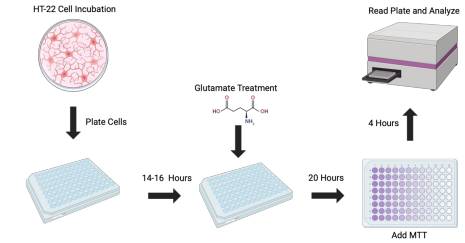

Figure 1. MTT assay.

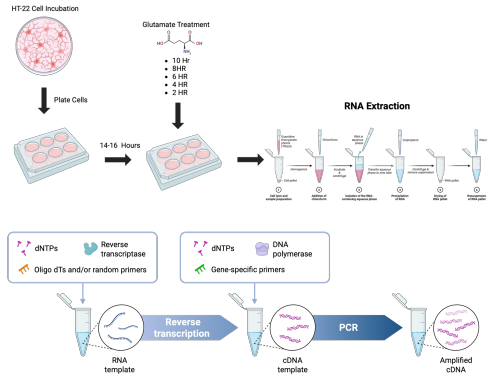

Figure 2. Gene expression analysis using RT-qPCR.

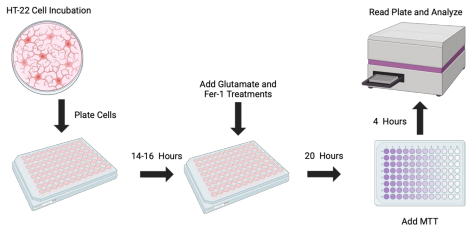

Figure 3. Ferrostatin MTT assay.

HT-22 Neuronal Stress Results

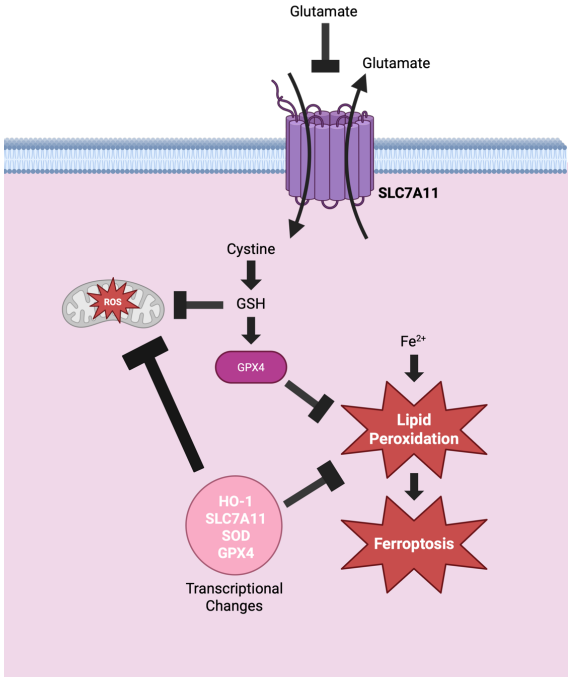

Figure 4. High glutamate induces iron-dependent ferroptosis via system xc⁻. High glutamate directly blocks the Scl7a11 cystine/glutamate antiporter. Intracellular cystine and GSH are depleted, inactivating the crucial antioxidant enzyme GPX4. Lipid peroxidation, fueled by Fe^{2+}, leads to ferroptosis. Transcriptional changes induce protective factors (HO-1, Slc7a11, SOD, GPX4, etc.) to attempt to attenuate the oxidative stress-induced accumulation of ROS and mitigate cell death.

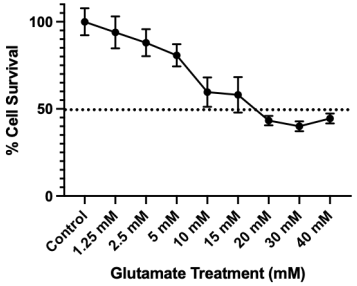

Figure 5. HT-22 Cell Viability with Glutamate Treatment. Cell survival decreases significantly as glutamate concentration increases, with the half-maximal inhibitory concentration falling between 15 mM and 20mM (dotted line). Mean ± SD (n = 3).

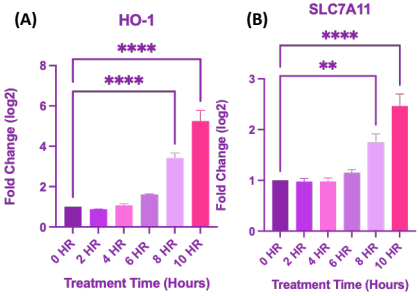

Figure 6. Time dependent induction of antioxidant gene expression. One-way ANOVAs revealed significant differences in (A) HO-1 and (B) Slc7a11 mRNA levels following glutamate treatment. Post-hoc analysis shows a robust, delayed transcriptional response beginning at 8 hours. Data represents mean ± SEM; ** = $p \leq 0.01$, **** = $p \leq 0.0001$ vs. 0 HR.

Conclusions

- Glutamate exposure induced oxidative stress in HT-22 neurons, reducing cell survival.
- Key antioxidant and ferroptosis-related genes (e.g. HO-1, Slc7a11) showed changes in response to stress.
- Ferrostatin partially protects cells, confirming lipid peroxidation contributes to cell death.
- These results demonstrate that oxidative stress triggers ferroptotic neuronal death in this model.

Future Directions

- Test potential protective compounds to see if boosting antioxidant defenses reduces ferroptotic cell death.
- Use ROS assays to quantify reactive oxygen species and link oxidative stress to ferroptosis.
- Investigate additional ferroptosis markers and signaling pathways.
- Explore combination strategies targeting oxidative stress and ferroptosis to protect neurons in Alzheimer's disease.

References

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