Regulation of Hippocampal Glucocorticoid Signaling by Mifepristone in the Context of Alcohol Dependence

Julia Kapusta, Sophia Marathonititis, Laura Monteagudo Romero, Kim Edwards, Scott Edwards
Louisiana State University Health Science Center Summer Program

Introduction

- Enhanced glucocorticoid signaling promotes hippocampal damage and facilitates the transition to alcohol use disorder (AUD).
- This study investigated excessive alcohol exposure and withdrawal, which is known to cause increases in glucocorticoid levels.
- The drug mifepristone, a non-selective glucocorticoid receptor antagonist, was explored as a potential therapeutic agent.
- We hypothesized that alcohol would increase glucocorticoid receptor signaling, determined by increased amounts of phosphorylated GR.
- We also predicted mifepristone would reduce phosphorylated GR to basal levels.

Results

Figure 3

C) Two groups of male rats were used. Eight rats were exposed to a vaporized alcohol environment for 14 hours a day for 10 weeks while the other twelve controls were exposed to normal air. For the last 3 of the 10 weeks, half of the alcohol-exposed group and half of the normal air group were treated with a 21-day, slow-release mifepristone pellet implant, while the other rats received a placebo pellet vehicle. Using the western blotting technique, we were able to track the differing levels of the phosphorylated glucocorticoid receptor protein as well as total glucocorticoid receptor levels.

Figure 4

D) Western analysis determined a moderate, but not significant, increase in GR phosphorylation in the hippocampus in alcohol-exposed male rats. Mifepristone did not alter the basal or alcohol-induced GR phosphorylation. There were no changes in total GR levels in any groups.

Figure 5

E) pGR and Total GR western blot data. Hippocampus samples were arranged in alternating order of control and experimental rat groups.

Conclusions

- Withdrawal from chronic alcohol vapor exposure led to modest increases in GR phosphorylation in the hippocampus of male rats, with no changes in total GR levels.
- This effect was not altered by mifepristone therapy, suggesting that mifepristone may work downstream of GR phosphorylation to influence hippocampal signaling.
- Future studies will determine whether these relationships are true in female rats, where we expect to see greater increases in alcohol withdrawal-induced GR phosphorylation.
- We will also be examining the effects of mifepristone to alter alcohol-induced changes in neuroinflammatory markers in future work.

In summary: We initially expected to see increases in pGR and no change in total GR levels. With these modest changes, it may be that the pGR increase is specific to a sub-region of the hippocampus. It may also be that we see larger changes in females. Also, if we see the same effect size in females, our results may become statistically significant after adding female animals to the analysis.

Materials & Methods

C) An illustration of the priming process.
- Glucocorticoids (purple) cross the cell membrane, enter the cell, and bind to GC receptors.
- Activated glucocorticoid receptors lead to the downstream activation of inflammatorymases.
- Upon a second stress stimulus, the primed cell releases pro-inflammatory cytokines—causing an excess of neuroinflammation.

B) An illustration of our prediction.
- If our hypothesis is correct, alcohol will increase glucocorticoid levels in the hippocampus—increasing glucocorticoid receptor phosphorylation.
- We also predict that mifepristone will prevent glucocorticoid-related signaling.

References

- Illustrations created via Biosmart.com

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