Julia E Kapusta
Sophomore Undergraduate
Boston University, Boston, Massachusetts

Mentor: Dr. Scott Edwards
LSUHSC, Department of Physiology, Comprehensive Alcohol-HIV/AIDS Research Center

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

Background and Purpose: Stress-related glucocorticoid signaling is known to damage vulnerable areas of the brain and promote the transition to alcohol use disorder (AUD). This study investigated hippocampal neuroadaptations produced by excessive alcohol exposure, as alcohol is known to increase glucocorticoid levels. Furthermore, the drug mifepristone, a non-selective glucocorticoid receptor antagonist, was also investigated to better understand its therapeutic potential. Under the hypothesis that alcohol dependence will lead to increased levels of glucocorticoid receptor (GR) phosphorylation as well as downstream neuroinflammatory markers (NLRP3/IL-1beta) in the hippocampus, our goal was to analyze mifepristone's potential to reduce these markers back down to levels seen in non-dependent animals.

Experimental Approach: In order to model individuals with AUD in comparison to non-drinkers, two groups of male rats were used. Eight rats were exposed to a vaporized alcohol environment for fourteen hours every day for ten weeks while the other twelve controls were exposed to normal air. For the last three of the ten 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. The rats were then sacrificed during acute withdrawal, and the hippocampus samples were analyzed using western blots. We were able to analyze both phosphorylated glucocorticoid receptors as well as total glucocorticoid receptor levels

Key Results: Withdrawal from chronic alcohol vapor exposure led to modest, non-significant increases in GR phosphorylation in the hippocampus of male rats, with no changes in total GR levels. This change was not modified by mifepristone therapy.

Conclusions and Implications: Because the phosphorylation effect was not altered by mifepristone therapy, our research suggests that mifepristone may instead work downstream of GR phosphorylation. Thus, in future studies we will be looking at NLRP3 and IL-1beta markers of neuroinflammation to test this prediction. We will also be looking at potential sex differences to determine whether the alcohol-induced increase of GR phosphorylation might be enhanced in females.