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"Modulation of Glutamatergic Signaling following Adolescent Alcohol Exposure in the Hippocampus of Male and Female Mice"

Exposure to alcohol during adolescence has been proven to increase the risk of developing an alcohol abuse disorder. This increased risk is due to alcohol effects on the developing brain. One way that alcohol can produce long lasting changes within the brain is by impacting the neural mechanisms of plasticity. A key mechanism involved in the induction of plasticity is through the regulation of glutamate and its receptors (specifically AMPA and NMDA receptors). The NMDA and AMPA receptors are composed of multiple subunits and these subunit compositions contribute to their functionality. Alcohol's short-term effects on NMDARs is to inhibit receptor transmission. However, long term alcohol exposure leads to a compensatory enhancement of NMDAR in adult rodents. Unfortunately, little is known about the long-term effects of glutamatergic signaling from exposure of alcohol during adolescence. In addition, little is also known about how these effects differ between the sexes since nearly all adult work has been done on male rodents. In the Wills lab, their focus has been to look at these effects of adolescent alcohol on glutamate signaling in the bed nucleus of the stria terminalis (BNST) in male and female mice. The BNST is an important brain region because it is a crucial region for negative affect and stress regulation, which are known causes for alcohol relapse and continued alcohol use. The lab has found that adolescent alcohol exposure (AIE) causes an increase in GluN2B and GluN1 NMDAR subunits, while no changes were found in the GluA2 AMPAR subunit in male mice. In addition, it was concluded that AIE produced enhancement of NMDAR-plasticity in males. Females did not show the same response to this treatment. In my current project, our objective is to see if sex specific effects on glutamatergic signaling were found across brain regions or specific to the BNST. One brain region that projects to the BNST and has well characterized glutamatergic signaling is the hippocampus.

To do this, we used a mouse model of adolescent alcohol exposure previously used by the lab. In this model, C57 male and female mice were given two four-day cycles of alcohol vapor (14hr in, 16hr out) interspersed by three off days. Then during acute withdrawal (five hours after final vapor exposure), brains were collected and then tissue samples were taken to isolate the hippocampus. The tissue samples were analyzed using Western Blot analysis for the NMDAR subunit (GluN2B, GluN1, GluN2A) and AMPAR (GluA2) and normalized to GAPDH. I In the hippocampus, there were no changes in NMDAR subunit (GluN2B, GluN1, GluN2A) or AMPAR (GluA2) in either male or female mice. This is in contrast to from results found in the BNST where NMDAR and AMPAR were differentially affected by AIE in males and females. This it can be inferred that glutamatergic signal in BNST is more vulnerable to adolescent alcohol exposure and sex specific effects than the hippocampus. Future work will expand this analysis to other brain regions and to determine mechanisms that lead to increased vulnerability in the BNST to AIE and sex differences.