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"Interactions of mGluR1/5 Transmission and CRF Signaling Following Adolescent Alcohol Exposure & Adult Stress"

Alcohol exposure in adolescence serves as a strong predictor of alcohol use disorder (AUD) in adulthood. Adolescence is time when alcohol drinking is commonly initiated and recent data points to sex differences in this consumption, with females consuming more alcohol during adolescence than males. Understanding the long-term consequences of adolescent alcohol exposure on neurocircuitry and behavior may help us identify the factors that increase AUD risk. Negative affect and stress are known to be common triggers for alcohol relapse and are also thought to be more powerful drivers for female drinking compared to male, whom are more likely to drink for the rewarding aspects of alcohol. The bed nucleus of the stria terminalis (BNST) is a sexually dimorphic brain region responsible for mediating negative affect and stress-induced drug relapse, making it an ideal target to study alcohol-mediated neuroplasticity. Our lab examines the effects of adolescent intermittent ethanol vapor exposure (AIE) and adulthood restraint stress on long-term plasticity in the BNST. Published work from our lab shows sex-specific alterations in excitatory transmission within the BNST after AIE treatment; in females this corresponded to altered group 1 mGluR signaling. These changes are recapitulated in adulthood following AIE only after a 1-hour restraint stress challenge, suggesting stress is a key mediator of this altered transmission.

Corticotropin Releasing Factor (CRF) is involved in alcohol withdrawal, stress-induced relapse, and withdrawal-associated negative affect. In the current study, we examined the effects of CRF signaling on AIE-induced sex-dependent plasticity in the BNST. We hypothesized that blocking CRF Receptor type 1 (CRFR1) signaling with a CRFR1 antagonist (1 µM NBI 27914) in BNST slices from mice that underwent AIE and adult stress would prevent the changes in mGluR plasticity previously demonstrated in female mice. Adolescent female mice were exposed to two four-day cycles of alcohol vapor for 16h/day (AIE), then aged undisturbed into adulthood, and finally received 1 hour of restraint stress on the day of experiment. Slices were then collected for slice electrophysiology. We found that AIE and adult stress produced an enhancement of DHPG-induced long-term depression (LTD) compared to controls. CRFR1 antagonism blocked this enhanced DHPG-induced LTD in AIE treated mice, without affecting DHPG-induced LTD in air controls. These results suggest a potential novel interaction of CRFR1 signaling on mGluR1/5-mediated plasticity in female mice following adolescent alcohol exposure. Future studies will further investigate the mechanisms involved in the CRFR1 and mGluR1/5 interactions in the female BNST.